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GYNECOMASTIA DUE TO INFECTIOUS HEPATITIS OF THE HOMOLOGOUS SERUM TYPE

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Clinical observations and experimental studies suggest that gynecomastia is due usually to a disturbance in hormonal activity. Although hyperestrinism may be the most important factor,[6,16] gynecomastia has also occurred after the administration of androgen[19] and desoxycorticosterone,[15,22] and in conditions associated with an increase in gonadotropic hormone,[5,7,14] and a decrease in the 17-ketosteroid[24] excretion. In the present state of our knowledge it is not known whether these observations indicate that gynecomastia can be produced by a variety of unrelated disturbances, or whether they all act through a common mechanism, possibly in the pituitary.

Clinical evidence of an endocrine disturbance is obvious in some cases of gynecomastia, as, for example, in those associated with tumors of the adrenals,[18,26] pituitary[29] and testes,[5,7] and in those occurring with puberty,[11] atrophy of the testes,[2,14] and hyperthyroidism.[28] In many cases, however, the endocrine system appears to be normal. As the physiology of the hormones is elucidated and as better methods of assaying hormone activity become available, it should be possible to determine the pathogenesis of all types of gynecomastia. This development is well illustrated in the case of the gynecomastia associated with cirrhosis, which has been recognized for a long time,[3] but which has only recently been found to be due to a disturbance in estrogen metabolism.[9]

It is reasonable to suppose that a similar disturbance may occur in other types of liver disease and may lead to gynecomastia. Indeed, an increased excretion of estrogen has recently been found in infectious hepatitis.[8] We now wish to report the occurrence of gynecomastia in 2 patients with this disease.

Case Reports Case 1. L. E. C., a 32 year old soldier, incurred a compound comminuted fracture of the left tibia when struck by an enemy shell fragment on Jan. 11, 1945. He was removed to a hospital where he received appropriate surgical treatment, including several infusions of plasma. On April 8 he was transferred to the Schick General Hospital for further surgical treatment.

The *past history* revealed a penile lesion with positive Wassermann reaction in 1937. Inadequate antisyphilitic treatment was administered for an indefinite period thereafter. In 1943 asymptomatic neurosyphilis,

with positive blood and spinal fluid, was discovered. A course of artificial fever therapy was given, the results of which are not known.

Physical examination on April 8, 1945, revealed nothing of note except an incompletely healed compound fracture of the left tibia and the residuals of frost-bite of the toes. The liver was not palpable and the genitalia were normal. No note was made of the condition of the breasts, but the patient, at a later date, maintained that they were normal at this time. There were no abnormal neurologic findings.

Laboratory studies revealed a normal blood count and urine. The blood Kahn test was positive. The spinal fluid exhibited Group I changes of neurosyphilis.

The patient's *course* in the hospital was uneventful during the 1st month. On May 14, approximately 4 months after the last infusion of plasma, he developed nausea, diarrhea and dark urine. Four days later clinical jaundice appeared and the liver was palpated 3 cm. below the costal margin. There was no hepatic tenderness and the spleen was not palpable. Studies at this time revealed a 1 minute serum bilirubin of 4.5 and a total serum bilirubin of 7.2 mg. %, a positive test for bile in the urine and normal prothrombin level. A few days later the serum proteins were found to be low with a normal albumin-globulin ratio. The thymol turbidity reaction and the sedimentation rate were normal. A diagnosis of acute homologous serum hepatitis was made. The patient was kept at complete bed rest and a diet high in carbohydrate and protein and low in fat was administered.

During the following 4 weeks the jaundice increased in intensity and there was marked lassitude, anorexia and weight loss. At no time was there nausea or vomiting. Shortly after the onset of jaundice the liver receded behind the costal margin and could never again be palpated. At no time was there splenomegaly, ascites or edema. Because of the anorexia and poor dietary intake, daily infusions of 1 to 2 liters of 10% glucose were given from June 4 to June 15. In addition. 25 gm. of concentrated human serum albumin were given intravenously on June 6, 7 and 8 and 500 cc. of plasma on June 9. The serum protein level, which was slightly depressed before treatment, showed a transient rise, especially in the albumin fraction. The prothrombin level fell slightly during the first 2 weeks of jaundice, but in the 3rd week it fell precipitously to 20% of normal. Although there was no bleeding from the skin or mucous membranes, vitamin K therapy was instituted. The patient received 8 mg. daily, intramuscularly, from June 8 to July 21. The prothrombin level rose very slowly, reaching 67% of normal in 3 weeks. In part, at least, the rise could be attributed to the improvement in liver function that occurred at that time.

The jaundice reached its peak at the end of the 4th week, by which time the total serum bilirubin had attained a level of 36.2 mg. %. From then on there was rapid improvement in the patient's general condition. All his symptoms subsided, his appetite returned, and he regained the weight he had lost. The jaundice, however, faded very slowly. Clinical icterus did not clear up until the 15th week of the disease and the serum bilirubin did not return to normal until the 22nd week. Although the patient felt well and there were no overt signs of liver disease, there was evidence of liver damage as late as 37 weeks after the onset of jaundice, as evidenced by the retention of 22% of injected bromsulphalein (5 mg. per kg.) at the end of 45 minutes. The liver and spleen were not palpable. There were no signs of portal obstruction. There were no spider nevi and no palmar erythema.

On July 1, approximately 7 weeks after the onset of jaundice and 3 weeks after it had begun to fade, the patient first noted symmetrical enlargement and tenderness of the breasts. They gradually increased in size over a period of 5 weeks. Examination at that time revealed slight fatty enlargement of both breasts. The nipples and areolas appeared normal and there was no secretion. A small, firm, tender nodule was palpable beneath each areola. The attending surgeon who saw the patient at this time believed the masses were fibro-adenomata and recommended excision. The patient, however, refused to submit to operation. During the following 8 weeks the enlargement and tenderness of the breasts gradually subsided, so that they no longer appeared abnormal. Nevertheless, a freely movable, moderately firm, non-tender and smooth mass, measuring 2 cm. in diameter, could still be felt beneath the areola of the

right breast as late as Feb. 11, 1946, 7 months after the onset of gynecomastia. At no time were there other stigmata of an endocrine disturbance. The patient was well developed physically. He exhibited no unusual distribution of fat. The beard and the hair on the trunk were of the normal male type. The external genitalia were well developed. The blood pressure remained normal.

The results of the liver function studies, briefly outlined above, are enumerated in Table 1.

note except for the left leg which was encased in a plaster cast. There was no obvious malnutrition, although the patient was not weighed. The genitalia were normal and there were no stigmata of any endocrine disturbance. No note was made of the condition of the breasts, although in retrospect the patient maintained that they were normal at this time.

Laboratory studies on admission revealed a normal blood count and urine. The blood Kahn test was negative. Culture of the wound yielded a heavy growth of penicillin-

TABLE 1.—LIVER FUNCTION STUDIES IN CASE 1

Date	1-min. serum bilirubin (mg. %)	Total serum bilirubin (mg. %)	Bromsulphalein retention (%)	Serum protein (gm. %)	Serum albumin (gm. %)	Serum globulin gm. %)	Prothrombin level (% of normal)	Cephalin-cholesterol flocculation	Thymol turbidity (units)	Hippuric acid excretion (gm.)	Urine urobilinogen (units)	Urine bile test
5/18/45	4.50	7.20	..	..	..	..	100	..	3			
5/21/45	..	..	..	4.80	3.80	1.00	75					
5/25/45	..	..	..	6.06	3.54	2.52	77					
6/ 8/45	21.20	36.10	..	6.02	3.61	2.41	20	+/1+	2	..	5.75	
6/11/45	22.20	36.20	..	6.15	4.35	1.80	37	..	3	0.32		
4/14/45	13.10	23.00	..	4.75	3.27	1.48	42	2+/3+	2	..	..	4+
6/26/45	..	..	..	4.83	2.87	1.96	67					
7/ 1/45	ONSET OF GYNECOMASTIA											
7/11/45	3.70	7.12	..	..	..	..	..	..	4			
7/28/45	1.42	2.90	..	..	..	..	..	..	3			
8/ 6/45	1.12	1.87	..	..	..	..	..	..	2			
8/15/45	0.75	2.25	..	..	..	..	..	..	2			
8/25/45	0.55	1.25	..	..	..	..	..	..	3			
8/31/45	0.45	1.07	..	..	..	..	..	..	1			
9/ 8/45	0.35	1.70	..	..	..	..	..	..	2			
10/15/45	0.15	0.60	23	..	..	..	..	..	2	..	0.34	
10/20/45	..	..	..	..	..	..	..	..	..	..	0.66	
10/22/45	..	..	..	..	..	..	..	..	..	..	0.63	
12/10/45	0.07	0.45	15	..	..	..	..	..	3			
1/29/46	0.07	0.70	22	..	..	..	..	..	3			

Methods employed described in previous communications.[12,20]
Normal values: 1 minute serum bilirubin = 0.2 mg. or less; total serum bilirubin = 1 mg. or less; bromsulpha ein retention at the end of 45 minutes (5 mg. kg.) = 5% or less; serum protein = 6 gm. or over; serum albumin = 4 gm.; cephalin-cholesterol flocculation = less than 1+ in 24 hours and 2+ in 48 hours; thymol turbidity reaction = less than 5 units; hippuric acid excretion (1.77 gm. sodium benzoate intravenously) = 0.7 to 0.9 gm.; urine urobilinogen (2 hour excretion) = less than 1.3 Ehrlich units.

CASE 2. E. J. P., a 28 year old soldier, incurred a compound comminuted fracture of the left calcaneus, astragalus and cuboid when struck by enemy shell fragments on Oct. 16, 1944. He was removed to a hospital where he was given multiple transfusions of whole blood and plasma. The following day the wounds were débrided. Since the posterior tibial artery was completely severed it was tied off. A week later secondary closure of the wound was attempted. The wound failed to heal completely, so that the patient was returned to the United States.

He was admitted to the Schick General Hospital on Jan. 19, 1945, at which time *physical examination* revealed nothing of

resistant *Streptococcus fecalis* and *Bacillus pyocyaneus*.

Course: On January 22, the cast was bivalved. Roentgenograms were taken and a new cast was applied. Immediately following this procedure the patient developed nausea and anorexia. A few days later the urine became dark in color, and on February 6 clinical jaundice became evident. The liver was enlarged 3 cm. below the costal margin and was tender. The spleen could not be felt and there was no fever. The total serum bilirubin was 7 mg. % with an immediate direct van den Bergh reaction. The cephalin-cholesterol flocculation reaction was 3+. The serum total proteins

were 5.5 gm. % with a relatively normal albumin-globulin ratio. A diagnosis of acute homologous serum hepatitis was made. The onset of symptoms had occurred 14 weeks after the last transfusion of blood and plasma.

A high carbohydrate, high protein, low fat diet was ordered for the patient, but he ate very little for the first 3 weeks, losing 20 pounds in weight. The jaundice increased in depth during the first 2 weeks and the liver increased in size, descending 8 cm. below the costal margin. On February 21, the total serum bilirubin reached its maximum level of 35.5 mg. %. There was a concomitant progressive deterioration of parenchymal function, as indicated in Table 2. During the period of poor dietary intake parenteral glucose, human serum albumin and vitamins were administered. At the height of the jaundice the prothrombin level of the blood fell. Large doses of vitamin K were given, but very little effect was noted.

On February 17, during the 4th week of hepatitis, the patient developed an acute, non-suppurative epididymitis on the right. Three days later he developed chills and fever, pain in the teeth and gums, and marked leukopenia. The leukocyte count was 1950 per c.mm., with 11% polymorphonuclears, 45% lymphocytes, 11% atypical lymphocytes, 14% monocytes; 15% eosinophils, and 4% plasma cells. The red blood cell count remained normal. There was a slight reduction in the platelet count to 170,000 per c.mm. There was no lymphadenopathy, splenomegaly or ulceration of the mucous membranes. The heterophil agglutination test for infectious mononucleosis was negative. Although a drug reaction was suspected it was not proved. The epididymitis healed completely within 1 week and was thought to be related to an attack of gonorrhea in the past. The patient was given several transfusions and large doses of penicillin, totaling 2,160,000 units, between February 18 and 24. The fever subsided in a few days and the blood count returned to normal a few days later.

Marked clinical improvement occurred following the subsidence of fever in the 6th week of the disease. Appetite returned and the patient began to gain weight. Hepatic tenderness subsided and the liver edge began to recede toward the costal margin. Jaundice, however, faded much more slowly and did not disappear until the 12th week,

TABLE 2.—LIVER FUNCTION STUDIES IN CASE 2

Date	1-min. serum bilirubin (mg. %)	Total serum bilirubin (mg. %)	Serum protein (gm. %)	Serum albumin (gm. %)	Serum globulin (gm. %)	Serum cholesterol (mg. %)	Cholesterol esters (% to total)	Serum alkaline phosphatase (units)	Prothrombin time (control:pt.) (sec.)	Cephalin-cholesterol flocculation	Thymol turbidity (units)	Urine bile test	Urine urobilinogen (units)	Hippuric acid excretion (gm.)
2/ 6/45	..	7.00	5.50	3.10	2.40	..	..	..	..	3+/4+				
2/ 9/45	..	..	..	..	..	..	..	..	14/14	..				
2/10/45	..	..	..	..	..	..	..	..	..	..	..	..	..	0.45
2/12/45	..	16.60	5.50	3.30	2.20	..	..	..	..	4+/4+				
2/15/45	17.00	30.70	..	..	..	..	..	9.9	..	3+/4+	8	4+	1.85	
2/21/45	19.60	35.50	..	..	..	..	..	..	15/21	2+/3+	9	2+	5.00	
2/26/45	13.40	24.50	6.05	3.10	2.95	170	15	20.0	14/22	2+/3+	7	4+	7.31	
3/ 1/45	20.00	29.00	..	..	..	..	..	17.0	..	3+/3+	8	4+	2.64	
3/ 3/45	12.50	27.50	..	..	..	..	..	15.1	..	3+/3+	9			
3/ 4/45	..	..	6.30	3.70	2.60	..	..	..	16/20	..	..	3+	37.00	
3/ 6/45	9.50	21.53	..	..	..	..	..	15.0	..	3+/4+	8	2+	28.80	
3/ 8/45	5.75	13.25	..	..	..	..	..	15.5	..	2+/3+	8			
3/10/45	5.75	12.00	..	..	..	213	46	12.0	..	2+/3+	8	1+	24.80	
3/19/45	3.00	6.50	..	..	..	220	62	12.8	..	1+/1+	6	0	2.80	
3/26/45	2.13	5.13	..	..	..	..	..	..	..	..	6			
3/27/45	..	..	..	..	..	..	..	..	..	..	..	0	4.95	
4/14/45	0.50	1.75												
4/19/45	0.65	1.00	..	..	..	..	..	..	..	..	3			
ONSET OF GYNECOMASTIA														
4/24/46	..	..	..	..	..	..	..	..	..	..	..	..	2.18	
4/26/45	..	..	..	..	..	..	..	..	..	..	..	..	4.24	
4/27/45	..	..	..	..	..	..	..	..	..	..	..	..	5.46	
9/21/45	0.10	0.45	..	..	..	..	..	..	..	..	1			

Normal valves as in Table 1; serum cholesterol = 150 to 250 mg.; cholesterol esters = 40 to 70% of total cholesterol; serum alkaline phosphatase = below 5 Bodansky units.

although the serum bilirubin level was still slightly elevated then. As indicated in Table 2, the return of liver function paralleled the subsidence of jaundice, although the excretion of urobilinogen was still abnormally high in the 14th week.

During April 1945, in the 14th week of the disease when jaundice had subsided but when a mild degree of impaired liver function was still present, the patient noted a painful enlargement of the right breast. Examination revealed a conical fatty enlargement of the breast with a circumscribed mass of moderately tender glandular tissue, about 4 cm. in diameter, beneath the areola. The mass was freely movable beneath the areola and over the underlying tissues, but appeared to be attached to the nipple. The areola and nipple were normal and there was no secretion. A month later an identical mass appeared in the left breast. The attending surgeon suggested the diagnosis of adenofibroma of the breasts and recommended excision. The patient, however, refused to submit to operation. The tumors showed no change for 2 months and then began to get smaller. The mass on the right disappeared in July 1945, about 3 months after is appearance. The one on the left was still present in September 1945, 4 months after its appearance. The liver was no longer palpable at this time and the serum bilirubin level and the thymol turbidity reaction were normal. Unfortunately no note was made of the condition of the genitalia.

Clinical Features of Gynecomastia Complicating Infectious Hepatitis. The structural changes in the breasts observed in these cases were typical of gynecomastia. Unfortunately biopsy specimens were not obtained, so that the characteristic hyperplasia of the ducts and periductile tissues[13,17] was not demonstrated. The bilateral involvement of the breasts and their regression later make the initial diagnosis of fibro-adenoma highly improbable. Chronic mastitis can be excluded for the same reason and also because the usual inciting factor, trauma, was absent.

There were many striking similarities between these 2 cases. In both the gynecomastia was bilateral, although in Case 2 there was a 1 month interval between its appearance on the 2 sides. There was a marked tendency toward regression. In Case 1 the gynecomastia had almost disappeared in 8 weeks, although small masses of glandular tissue could still be felt as long as 7 months after the onset. In Case 2 it cleared up completely on one side within 3 months, while on the other a small mass was still present at the end of 4 months. Breast enlargement occurred late in convalescence from hepatitis; in Case 1, 7 weeks after the onset of hepatitis and at a time when jaundice had largely subsided, and in Case 2, 14 weeks after the onset when clinical jaundice was no longer evident.

The hepatitis was of the homologous serum type in both instances, and, as is often the case in this form of the disease,[23,27] it was unusually severe, ran a protracted course, and was followed by residual impairment of liver function. In Case 1 the serum bilirubin attained a level of 36.2 mg. %, clinical jaundice lasted 15 weeks, and there was marked bromsulphalein retention at the end of 37 weeks. The peak of the serum bilirubin level in Case 2 was 35.5 mg. %, clinical jaundice lasted 12 weeks, and the urinary excretion of urobilinogen was still moderately increased in the 14th week. The occurrence of residual impairment of liver function following jaundice of this severity and duration is not surprising in the light of recent experience.[12] There were no physical findings, however, to suggest the development of cirrhosis, a complication of hepatitis encountered occasionally.[4] In neither case could the liver be felt during convalescence, and there was no evidence of collateral venous circulation, splenomegaly, ascites, spider nevi or palmar erythema.

Comment. The normal liver inactivated estrogen,[30] but in experimental liver injury[1,10,25,29] and in clinical cirrhosis[9] this function is seriously impaired. The gynecomastia that occurs in cirrhosis is thought to be due to the resultant hyperestrinemia,[9] but other factors may be contributory. Certainly atrophy of the

testes[21] and chronic malnutrition, which are common complications of cirrhosis, may play a rôle, since both may give rise to gynecomastia in non-cirrhotics.[2,13,14,24]

It is surprising that, with the recent increase in the incidence of infectious hepatitis, gynecomastia has not, heretofore, been reported as a complication. It is noteworthy, however, that both our cases suffered unusually severe and protracted jaundice. Evidently the factors responsible for growth of the breast must be operative over a long period or must come into play only after unusually severe liver damage to produce gynecomastia.

Cirrhosis and infectious hepatitis, especially when the latter is severe, share a common background of diffuse injury to the liver with a marked disturbance in many of its functions. It appears likely, therefore, that the pathogenesis of the gynecomastia that occurs in both conditions is the same. Unfortunately it was not possible to study hormone excretion in our cases. The recent work of Gilder and Hoagland,[8] however, suggests that hyperestrinemia is an important factor. They have found that there is an increase in estrogen excretion during the acute phase of infectious hepatitis in males, and that the increase is proportional to the severity of the disease. During convalescence the excretion rate falls, but does not reach normal for some time.

Just as in cirrhosis, atrophy of the testes and chronic malnutrition may contribute to the development of gynecomastia in infectious hepatitis. Although the testes appeared normal, a decrease in 17-ketosteroid excretion has been noted in this disease,[8] suggesting that some degree of atrophy may have been present in our cases. Moderate weight loss occurred at the height of the jaundice, but the low initial serum protein levels (Tables 1 and 2) suggests that malnutrition was present even before the onset of hepatitis.

Since the breast lesion described subsides spontaneously, it is of importance to recognize its relationship to infectious hepatitis if needless surgery is to be avoided. The relationship is of particular interest to endocrinologists, since it affords a unique opportunity to study the pathogenesis of gynecomastia.

Summary. Bilateral gynecomastia occurred during convalescence in 2 cases of infectious hepatitis. The hepatitis was of the homologous serum type and ran a severe and protracted course, but there was no evidence to suggest the development of cirrhosis. The gynecomastia subsided spontaneously, so that early recognition of the relationship between breast lesions and hepatitis will preclude needless surgery. Hormone excretion studies in infectious hepatitis suggest that hyperestrinemia is an important factor in the pathogenesis of this type of gynecomastia. Testicular atrophy and malnutrition, however, may be contributory factors.

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VARIOLATION AS A PRINCIPLE

IMMUNIZATION IN EXPERIMENTAL POLIOMYELITIS WITH ACTIVE VIRUS UNDER AUTARCEOLOGIC PROTECTION OF ESTROGENIC SUBSTANCE

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VARIOLATION is perhaps the oldest specific immunizing procedure. In spite of what, from the present-day point of view, was an enormous hazard it was widely used and during a whole century the subject of continuous investigation. With many attempts to make it safe by preparation of the patient, such as by the use of the cooling regimen of Sydenham so that the "solids and fluids may be reduced from a greater to less inflammability," as well as by modification of the virus to be inoculated by dilution or the use of unripe virus, it might well have led to an efficacious preventive procedure had it not been supplanted by vaccination, and declared a felony by act of Parliament in 1840.[17] If "it might have led to an efficacious preventive procedure" could be said of smallpox where subclinical immunization does not occur naturally, variolation as a principle (immunization through mild disease by inoculation of the "prepared" patient with active virus) should offer even greater possibilities in disease where subclinical immunization is the rule and disease the exception. But it has entered little, if at all, into later immunologic investigation. Certainly the central idea in artificial immunization has been modification or attenuation of virus. Little attention has been paid to "preparation of the patient."

If variolation was outlawed a little over a century ago, variolation as a principle (using the term in the same sense that Pasteur used Jenner's specific term "vaccination" to designate a general principle) may be coming back on the scene at this precise time. Premarital exposure of females as a practicable preventive measure for the recently discovered congenital anomalies as a sequel to maternal rubella has been discussed in a recent paper.[11]

There are a number of examples of immunization where either advantage is taken of the prepared host, or where the procedure in a sense amounts to preparation of the host, though these procedures are perhaps probably more often looked upon as being in keeping with the legendary idea of "immunity from repeated bombardment with small subinfective doses." The first of these would be represented by measures aimed at the postponement of measles to an age when there is less likelihood of complications, that is, to an age when the patient is better "prepared" to withstand the attack. When looked at somewhat in reverse, the administration of convalescent serum or gamma globulin at the appropriate time after exposure to bring about a modified but immunizing attack of the disease, can likewise be regarded as an example of preparation of the patient. Another procedure which may actually amount to preparation of the patient, rather than modification of virus, is the employment of the interference phenomenon as in the use of complex vaccine in influenza. Ziegler and Horsfall[22] concluded that the first virus inoculation interferes with the multiplication of the second, not by multiplication *per se* nor by the action of one virus on the other, but probably resistance to the second virus is the result of a tissue alteration induced by the first virus.

Still another field, as yet quite unexplored, is that of biochemical interference.[10] It is not inconceivable that there may be inert substances with a chemical configuration and tissue tropism which would blockade a given but damaging virus-cell union (for example anterior horn cell in poliomyelitis) while immunization is being accomplished with active virus. Protective action of trypan red and certain related dyes against infection with certain neurotropic viruses has been shown although the mechanism involved was not elucidated.[21] In other words there is reason to believe there may be "heterologous" (chemical) as well as "homologous" (virus) interferants. Not inconsistent with the clinical observations of almost every investigator who has seen large numbers of cases, from Underwood in 1789 on, to the effect that poliomyelitis exhibits a preference for those "of strong and blooming constitution;" and in keeping with both the early observation of Rous[19] and the recent work of Schneider which more exactly assigns the rôle of dietary deficiency in susceptibility to infection,[20] new evidence that nutritional deficiency decreases susceptibility is at hand. The enhanced resistance of animals on dietary deficiency to a number of virus infections[16,18] is an example of "preparation of the host" where the development of immunity has not been investigated.

There are indications that in poliomyelitis factors in the host, rather than virus or exposure factors, may be a major determinant as between the development of the frank disease or of subclinical immunity upon exposure to the virus. Studies of the nature of these autarceologic factors[2,4,5,6,7,8] have led to experiments in which monkeys have been rendered more resistant to intranasal instillations of virus by administration of estrogenic substances.[3,4] That these experiments do not exactly reflect the mechanism of subclinical immunization in man, in spite of the fact that intranasal instillation presumably is a method of inoculation of virus simulating natural infection, is indicated by failure of even repeated intranasal instillations of virus under the protection of estrogenic substances to immunize. As with intranasal chemical blockade[9] this failure to immunize suggests that in such experiments a complete blocking of entrance of the virus is accomplished. In the disease in man where the indications are that a single infection results in immunity, it would appear that the virus must reach some deeper structure to set up the immunizing process. That the locus of estrogen-induced resistance is not the central nervous system itself is shown by the fact that under its influence animals, although resistant to intranasal instillation, are fully susceptible to intracerebral inoculation.[13] In earlier experiments[12] it had been found that active virus injected subcutaneously or intracutaneously frequently resulted in immunization with relatively little hazard of disease. It would now appear therefore, that in experiments on enhancement of resistance to disease where immunization is the objective, a route of inoculation lying somewhere between intracerebral and intranasal instillation should be employed.

The present paper reports the effect of administration of alpha-estradiol benzoate* on resistance of the mouse to *subcutaneous* injection of Mouse-Hamster strain[14] of poliomyelitis virus.† At the same time the possibilities of producing subclinical immunization rather than clinical disease by inoculation of the prepared host with active virus are investigated.

Experimental. *Effect of Alpha-estradiol Benzoate on Resistance.* One hundred normal albino mice weighing about 15 gm. and evenly divided as to sex were used in this experiment. Fifty were given a subcutaneous injection of 0.01 mg. of *a*-estradiol benzoate 3 times weekly. The remaining

* Progynon-B. Product of Schering Corporation.

† Anderson and Bolin[1] have reported enhancement of resistance to oral administration of the same virus by progesterone (complete protection), stilbestrol (mortality reduced from 68 to 2.5%), t-propionate (68 to 20%); desoxycorticosterone acetate failed to modify mortality.

mice received no treatment. Fourteen days after the initial injection of estrogen all mice were given a single subcutaneous injection of 0.02 ml. of a 10% emulsion of poliomyelitis virus prepared from brain of mice succumbing to the disease 4 to 5 days after inoculation. The results are shown in Chart 1. Sixty-two % of the prepared mice succumbed as compared with 84% of the untreated controls, a difference of exactly the same order as that obtained when intranasal instillation was employed.[15] Estrogen treatments were discontinued 11 days after virus injection and the surviving mice were later challenged for immunity.

Ten of the treated and 4 of the untreated mice withstood a third virus injection. The remaining mice were sacrificed and the blood sera collected for test for neutralizing substance.

Virus Neutralization Tests. The collected sera from mice that had received estrogen treatment and from untreated controls (all of which had withstood intraperitoneal challenge for immunity) were pooled separately. A third pool was made of normal mouse serum (serum controls). Each pool was thoroughly mixed with an equal amount of a 10% emulsion of poliomyelitis virus in a quantity sufficient to inject each of 6 mice

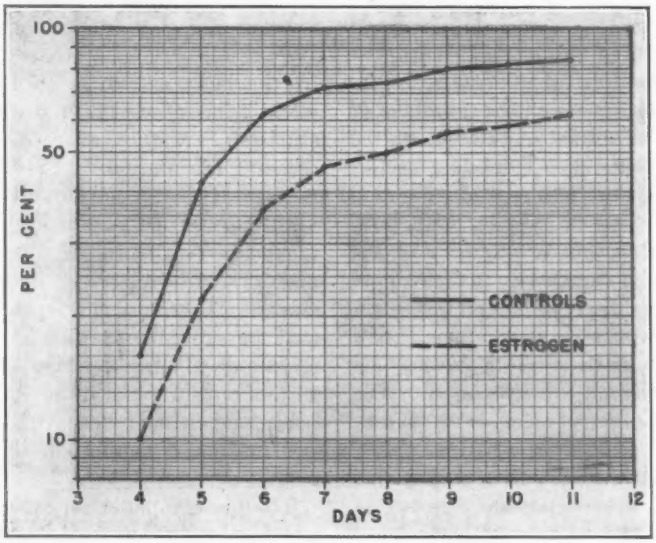

CHART 1.—Cumulative mortality. Estrogen treated and untreated control mice injected subcutaneously with M–H strain of poliomyelitis virus.

Intraperitoneal Injection of Virus as a Test for Immunity. Twenty-six days subsequent to subcutaneous injection of virus (15 days after the last mouse came down with the disease) all surviving mice, 19 treated and 8 untreated, were injected intraperitoneally with 0.05 ml. of a 10% emulsion of the same virus strain previously used. That this was a suitable challenge procedure for immunity is assured by the fact that normal mice given a like injection of the virus died with a mortality rate of 80 to 100%. None of the mice developed the disease. Fourteen days later the same mice were given a second intraperitoneal injection of 0.05 ml. of virus and all were still insusceptible to infection.

with 0.1 ml. of the mixture. For virus control, normal salt solution was used in the same manner as the pooled sera. The mixtures were incubated for 2 hours at 37.5° C. refrigerated overnight at 6° C. and then injected intraperitoneally into normal albino mice. The 12 mice injected with a mixture of serum from the resistant mice and virus did not develop the disease, whereas of the 12 mice injected with normal mouse serum or normal saline and virus mixtures, 11 developed paralysis and succumbed.

A summary of the tests for immunity show that 26 days after receiving a single subcutaneous injection of active virus all mice were insusceptible to infection as evi-

denced by failure of intraperitoneal injection of virus to produce the disease. A second and third similar test after 40 and 54 days showed a like result. On the latter day sera from these mice neutralized the virus *in vitro*.

Summary. In both estrogen prepared and untreated control mice subcutaneous injection of active poliomyelitis virus, when not resulting in the frank disease, produced subclinical immunity. However, a greater proportion of estrogen treated mice failed to develop the disease and consequently the number of mice that developed subclinical immunity was greater than in the controls. Hence, preparation of the host with estrogenic substance effected a decrease in production of disease by active virus, and an increase in occurrence of subclinical immunization.

These experiments represent an approach to immunization through the use of a new, albeit old, principle whereby subclinical immunization rather than clinical disease is produced by inoculation of the prepared host with unmodified virus, rather than by the now conventional method of inoculation of the unprepared host with modified or attenuated virus. Even though a procedure such as administration of estrogenic substance would produce an autarcetic state, it might not be feasible to maintain such a state of resistance by its continued use. It might be possible, however, to produce a temporary period of resistance during which subclinical immunity could be safely induced with active virus.

Neither these experiments nor any of the other examples of enhancement of host resistance to experimental infection cited begin to approach present-day standards of safety, though in this respect they are probably all superior to variolation as practiced a century ago.

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INFLUENZA AT AN ARMY CAMP IN 1945-1946

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During the fall of 1945, there was an epidemic of acute respiratory disease at Fort Benjamin Harrison. This epidemic was partly due to the virus of influenza B, as proven by serologic studies, but included cases clinically similar to influenza in which no rise in antibodies against the influenza viruses was found. Furthermore, the epidemic at the army post preceded the nation-wide influenza epidemic by several weeks. The purposes of this paper are: (1) to describe the course of the epidemic at Fort Harrison; (2) to outline a simplified variant of the familiar chick-cell agglutination inhibition test for influenzal antibodies; (3) to discuss the epidemiology of influenza as related to this outbreak; and (4) to discuss certain observations made by us in the course of the epidemic.

Methods. (*a*) Statistical. Statistical studies were based on acute respiratory diseases in general (Collins[3]). The term is here used to include colds, influenza, nasopharyngitis and other common respiratory diseases, as well as pneumonias. Rates are calculated as hospital admissions per 1000 per annum. The data for Fort Harrison were taken directly from the records on the wards; the rates for "U. S. Military" were taken from the Weekly Health Reports published by the Surgeon-General's Office.

(*b*) Laboratory. Serologic studies for antibodies against influenza viruses were performed by a virus dilution method of the chicken cell agglutination inhibition test.

Fresh chicken cells were washed 3 times, packed and diluted with saline to make a 2% suspension. They were kept in the icebox and never used after the 3rd day. *Virus* was prepared by inoculating 10 to 11 day eggs, and harvesting the allantoic fluid 2 days later. The product of each egg was tested for hemagglutinins by allowing a small amount of fluid to mix with the embryo's red cells on the bottom of a Petri dish. The fluids of several eggs were pooled and the product stored in large test tubes at 4° C. *Human sera* were obtained early in the disease, and again 7 to 14 days later from each case.

Procedure for the test was as follows: Twofold dilutions of virus-allantoic fluid in saline were first prepared in large test tubes, ranging in final dilutions from 1:16 to 1:2048. Then, 0.25 ml. of each dilution was added to Kahn tubes which were set in series in large racks. The serum was diluted by adding 0.2 ml. of serum to 3.8 ml. of saline, and to this was added 4 ml. of the 2% chicken cell suspension. The resulting serum-chicken cell combination was thoroughly mixed, and 0.25 ml. added to each Kahn tube with virus. After adequate shaking, the tubes were allowed to stand at room temperature for 1 hour. Tests were read according to the cell sedimentation pattern in the bottom of the tube. The tube was called positive if the pattern was diffuse; negative, if the cells were in a central button which would run when the tube was tipped, and ±, if of an intermediate form. The principle of titrations using a constant amount of serum against decreasing quantities of virus was employed by us on occasions in animal neutralization tests. Such a method has the advantage of measuring the effect of antibody on a virus endpoint determined at the time of the serologic test rather than a predetermined virus endpoint which may vary between the time of the original virus titration and the test. A virus dilution method for determining inhibiting antibodies with the use of human type "O" cells was employed by another group of workers.[4]

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Each serum was titrated against the PR8 strain of influenza A virus, and the Saha strain of influenza B virus. (The Lee strain of influenza B was also used in most titrations; results with it were similar to those obtained with Saha virus.) A control without serum was run routinely as a virus titration, and also known positive chicken sera against both influenza A and B were included. The early and late specimens from the same patient were run simultaneously.

The extent of reduction of the hemagglutinating capacity of a virus by the constant dilution of serum (1:80) determined the serum titer which was calculated as the ratio of the greatest dilution of virus *without* serum giving a ± reading, to the greatest dilution of virus giving a ± reading in the presence of the serum. For example: If the control was ± in the 7th tube (virus dilution 1:1024) and the serum-virus was ± in the 4th tube (virus dilution 1:128) the titer was 8. Whenever the transition was directly from positive to negative the endpoint was considered to be half-way between the last positive and the first negative tube. Repeated tests by this method gave consistent results. A patient was considered to show serologic evidence of influenza if there was at least a 4-fold rise in titer, on comparing the late with the early specimen.

COURSE OF THE EPIDEMIC. The numbers of hospital admissions for common respiratory diseases and pneumonias at Fort Benjamin Harrison from June 1945 to February 1946, by week of admission, are given in Table 1. It will be seen that the hospitalization rate for respiratory diseases from June to mid-September was low. Then, during the 3rd week in September, the rate suddenly rose and continued to rise until it reached a peak in early November. Following this, the rate declined and reached a low level by late December. The epidemic may be described as a distinct peak in the respiratory disease incidence, covering a period of about 15 weeks, with its crest in the 8th week.

The outbreak at Fort Harrison reached its peak and had begun to decline before the morbidity in the U. S. Army began its rise. The available evidence on influenza in Indiana and the U. S. civilian population in general (figures reported by the Indiana State Board of Health, and the U. S. Public Health Service Reports) shows that the sharp rise in the civilian rate came in late November, about the same time as that for the U. S. Army in general. All 3 were about 2 months after the rise in respiratory disease at Fort Harrison.

CLINICAL STUDIES. (*a*) *Cases Showing Definite Evidence of Influenza B.* There were 41 cases which showed serologic evidence of influenza B. The average age was 25 years; only 1 woman was included. Their distribution by age, sex, length of time in service, rank and unit was about that which would be expected with random distribution on the post. On the average, the men had been sick about 2 days before entering the hospital; this was usually because they had tried to "fight it out" before reporting sick. On admission, their commonest complaints were general malaise with muscular aches and with backache (68%), "feverishness" (63%), a sore throat (56%) and headache (56%); 44% had some other complaints such as chest pain on deep inspiration, nausea, diarrhea, dizziness, aches in the eyeballs, anorexia or hoarseness. Disorientation was observed in 1 patient who had been hospitalized several months for non-union of a fracture sustained in combat. The average admission temperature was 101° F., and the average admission pulse 94. The highest temperature noted on any proven case of influenza at any time was 103.6° F.

Physical examination showed most all the patients to have mild prostration, a flushed face, a reddened throat and moderately enlarged tonsils. Coryza and nasopharyngitis were noted in 93%; the pharynx usually showed moderate injection, with the venules engorged but without the extreme reddening often noted in streptococcal sore throat. Cervical adenopathy was present in 22%, a dry cough in 59%. Profuse sweating, which usually came on at night, was observed in 34% of the

cases. Other signs such as conjunctivitis, râles at the lung bases, tonsillitis, epistaxis and extreme prostration were seen in 1 or 2 cases. Complications were rare and unrelated to the disease.

The routine care of the cases was simple. It consisted of bed rest, forced fluids, regular diet, acetylsalicylic acid—acetophenetidin—caffeine tablets for aches, sleeping tablets if desired, neosynephrine nose drops to be taken by the patient 3 or 4 times a day, saline gargles, and elixir of terpene hydrate with codeine for cough. Sulfadiazine or penicillin was given to 10 patients for a brief time with no demonstrable effect. The course of the disease was uneventful in all cases. Assuming that fever began with the onset of symptoms, fever of 99° F. or over lasted from 2 to 8 days, with an average of 5 days. The average hospital stay was 11.6 days, with 6 and 28 days the extremes. Routine laboratory studies revealed the following. The admission white blood count averaged 6317, ranging from 4500 to 10,000. The polymorphonuclears averaged 63.5%, with extremes of 32% and 78%. Beta hemolytic streptococci were identified in 4 of 29 throat cultures. The results of serologic tests on acute and convalescent sera are summarized in Table 2, with Table 3 demonstrating the titer ratios of the convalescent to the acute blood specimens. It will be seen that, except for a single case which will be discussed later, there were no significant changes against influenza A (PR8 strain). In contrast to this, the mean titer against influenza B (Saha strain) rose from 3 in the acute sera to 37.9 in the convalescent sera, a mean rise of 12.9-fold.

(*b*) *Cases Not Showing Definite Evidence of Influenza.* As stated above, serologic tests were not generally considered significant for influenza unless there was a 4-fold rise in titer of the antibodies. There were 30 influenza suspects who did not show this rise. Of these, 8 showed a 1 tube (2-fold) rise in titer against influenza B and were considered serologically questionable cases. Analysis of their clinical course shows no significant differences from the definite cases.

There were 22 paired specimens in which not even a 1 tube difference was found. Ten of these had relatively high titers against one or the other of the influenza viruses used in the tests. In 3, this might be explained on the basis of previous vaccination. The mean titers of the 8 questionable cases, and the 22 cases with no antibody rise are shown in Table 4, along with the mean titers of the definite cases of influenza, a group of 29 normal prisoners who had not been vaccinated, and 15 normals who were vaccinated.

TABLE 1.—COMBINED RATES OF ACUTE RESPIRATORY DISEASES

(Calculated as hospitalizations per 1000 per annum)

Week ending	Ft. Harrison Military rate	U. S. Military rate	Week ending	Ft. Harrison Military rate	U. S. Military rate
June 8	28	118	Oct. 5	89	78
15	30	107	12	118	91
22	43	103	19	173	90
29	25	101	26	178	95
July 6	6	88	Nov. 2	215	92
13	34	84	9	232	96
20	38	88	16	189	98
27	26	86	23	208	113
Aug. 3	33	87	30	140	161
10	43	85	Dec. 7	116	182
17	33	82	14	40	183
24	33	91	21	65	170
31	29	89	28	7	158
Sept. 7	46	79	Jan. 4	59	171
14	34	74	11	29	200
21	92	80	18	7	181
28	101	82	25	16	195

(c) *A Case With Serologic Response Against Both A and B Viruses.* One patient showed a strong serologic response to both Type A and Type B influenza viruses. Review of his history showed that he had had malaise, chills, fever and headache on the train while *en route* to Fort Harrison. Several others on the same train had had the same symptoms, and 2 of his close companions from the trip were bled. Both had high titers against influenza virus Type A, and 1 gave a story of headache and shaking chills on the train. Although these findings are not conclusive, it is possible that all 3 contracted influenza A before arrival at the post. Still, one must not overlook the possibility of an anamnestic reaction. No other cases of influenza A were found. The man who appears to have been infected by both types of influenza in rapid succession was no sicker than the average case infected with Type B alone.

EPIDEMIOLOGY AND GENERAL DISCUSSION. *The Source of the Epidemic.* The source from which influenza B virus reached Fort Harrison was of primary interest. The fact that men were arriving from all parts of the country suggested that it had been imported. Yet careful examination of the cases by units showed that the respiratory disease rate rose at about the same time in the major units on the post. Included were such diversified groups as general prisoners, who were closely confined, and new recruits who went to the Indianapolis theaters in great numbers. The appearance of the outbreak on the military reservation earlier than in the civilian population was somewhat analogous to the situation in 1918 (Sydenstricker[8]).

The Commission on Acute Respiratory Diseases[1] suggested that "influenza persists in large populations through sporadic cases and limited outbreaks only to return

TABLE 2.—SEROLOGIC TESTS FOR INFLUENZA

	Recorded titer														Mean titer
	1*	1.5	2	3	4	6	8	12	16	24	32	48	64	96	
Frequency of titers *vs.* PR8 virus in 1st specimen	1	11	5	7	4	2	..	..	5	3	1	1	1	..	4.3
Frequency of titers *vs.* PR8 virus in 2nd specimen	2	7	6	8	3	3	..	1	5	3	1	1	1	..	4.6
Frequency of titers *vs.* Saha virus in 1st specimen	2	2	13	9†	12	..	..	2	..	1	..	..	..	..	3.0
Frequency of titers *vs.* Saha virus in 2nd specimen	..	..	..	..	1	..	2 and 2+‡	..	5	..	6 and 4+	6† and 3+	6 and 3+	2 and 1+	37.9

* Titer expressed as the fold reduction of virus activity by a 1:80 dilution of serum based on red cell agglutination-inhibition reaction.

† One set of sera was tested with Lee instead of Saha virus yielding titers of 3 on the 1st and greater than 48 on 2nd specimen.

‡ Number of specimens with titer greater than that expressed.

TABLE 3.—RISE IN ANTIBODY TITER IN CONVALESCENT SERUM SPECIMENS

	Titer ratio															Mean rise
	0.1–0.9	1	1.1–1.9	2	3	4	6	8	11	12	16	21	24	32	48	
Frequency distribution of titer changes to PR8 virus	6	29	3	2	..	..	..	..	..	..	1	..	..	..	..	1.1
Frequency distribution of titer changes to Saha virus	..	..	..	..	..	6	3	6	3	2	5	3	7	4	2	12.9

TABLE 4.—MEAN TITERS OF VARIOUS GROUPS

Group	Cases	Titer *vs.* PR8		Titer *vs* Saha	
		Early	Late	Early	Late
Definite influenza	41	4.3	4.6	3.0	37.9
Questionable influenza	8	3.8	3.5	3.5	7.4
Not proven influenza	22	5.9	5.7	5.2	4.6
Normal prisoners	29	2.5	..	4.7	..
Normals, vaccinated	15	2.0	37.0	4.5	11.9

in epidemic form when the necessary conditions are present which favor rapid dissemination of the agent." Such a limited outbreak occurred at Camp Atterbury, about 35 miles from Fort Harrison, in May 1945. The Saha strain of influenza B virus was isolated there (Sigel *et al.*[7]) and it was suggested that "although the outbreak referred to may remain an isolated episode, the possibility exists that it may represent the beginning of an epidemic wave of Type B etiology. The situation may parallel the experience of 1943, when an epidemic of influenza Type A was preceded by a localized outbreak of influenza in an army camp, from which Salk, Menke and Francis isolated a Type A virus." It is now suggested that Type B virus persisted in the Indianapolis region through sporadic or inapparent cases from May 1945 until its recognition in epidemic form in the fall of 1945. This suggestion is strengthened by the fact that an isolated interepidemic case of influenza Type B was diagnosed at Fort Harrison in July 1945.

Shope[6] has reviewed the relations between human and swine influenzas. A few swine on Fort Harrison were sick with a respiratory disease and the possibility that the human disease had come from an animal reservoir was investigated. Accordingly, 4 hogs were bled in the early days of their disease, again after they had recovered, and their blood tested. These tests were carried out against PR8, Saha and a British swine strain of influenza virus. No evidence of influenza was found.

Factors Influencing the Spread of Influenza. A second major point of interest was the method of spread within the camp. The arrival of many new men on the post was mentioned above. This increase alone does not adequately describe the changes, for there was not only an increase in new men, but an enormous rate of turnover. The onset of the epidemic followed almost immediately after this rapid turnover of personnel began.

Review of the daily temperature at Indianapolis reveals that there was a brief drop in the temperature at just about the same time as the population and respiratory disease rates began to rise. This cool period was not severe but the drop in temperature might have been a provoking factor in the outbreak. It might have contributed to the spread of the disease by keeping men inside the barracks. Because the men were quartered in large rooms which sometimes held over 100 men, considerable opportunity for contacts was present within each sleeping room. This was accentuated by the turnover and the natural tendency for men to get acquainted.

The difference between conditions which lead to a high effective contact rate and overcrowding as judged by the distance between beds or spaces at the dining table deserves emphasis. Repeated inspections never revealed beds which were closer than 30 inches, and the places at the mess halls did not seem too crowded. Nevertheless, the increased size of the post population greatly increased respiratory contacts. Movie theaters were crowded. Men swarmed into Indianapolis to see a new town by the only regular means of transport, a bus line. Although some extra vehicles were put on, these were not enough to accommodate all passengers. At the peak hours, every bus was filled to absolute capacity with men from all parts of the camp, who thus spent 45 minutes exchanging respiratory flora. Since the same mess halls had to serve an increased population, they were filled to capacity. In brief, there was a marked increase in the respiratory contacts per man per day both on the post and on trips to Indianapolis, even though regulations of bed space, table space and classroom space were met.

Factors Leading to the End of the Epidemic. A third topic of major interest was the factors which led to the decline of the epidemic at Fort Harrison. Probably several factors were responsible. At the peak of the epidemic the hospitalization rate for respiratory disease was 232 per 1000 *per annum.* There were probably

many subclinical or mild cases which were not hospitalized. The influx of new inductees slowed greatly in mid-November, and soon after that the strength declined. At about the same time, soon after the peak of the epidemic, a program for the vaccination of all men on the post, against influenza, was instituted. The response to the B component of the lot of vaccine used at Fort Harrison as measured by tests with the Lee and Saha viruses was not as great as that in soldiers in other posts studied by us. Still the increase in antibody level of the post population resulting from vaccination and from clinical as well as subclinical infections was probably another factor.

Other Respiratory Diseases. A situation which favors the spread of one respiratory disease usually favors the spread of others. Yet, bacterial infections were notably scarce at Fort Harrison. No cases of streptococcal or staphylococcal pneumonia were seen; while measles, mumps, German measles and atypical pneumonia were notably rare. There was a barely perceptible increase in pneumococcal pneumonia, but it was impossible to tell whether these were secondary to influenza or not.

As mentioned previously, a number of patients showed no serologic response to the influenza viruses. It may be that they had influenza, but that they either did not form antibodies or that their antibodies were not demonstrated by the test. We doubt that many cases are to be explained on this basis. Walks through the barracks in the evening, or inspection of messes, revealed many men with respiratory infections who did not report to sick call. At first we thought we could distinguish among these a syndrome which we called "scratchy throat" and which seemed milder than influenza, without its generalized aches, with a somewhat longer course, with an incubation period over 4 days, characterized by a red, scratchy throat. Throat cultures, antistreptolysin studies and influenza studies were essentially negative. Later, we found that we could not distinguish "scratchy throat" from influenza B on clinical grounds. The Commission on Acute Respiratory Diseases[2] also found that there were many cases of acute respiratory disease in which they could not make a specific diagnosis, and used the term ARD for these. In view of the Commission's findings, it is our opinion that "scratchy throat" was a separate entity which was present at the same time as influenza B and that it may have been identical with the disease called ARD by the Commission.

Relation to Other Outbreaks of Influenza. The Fort Benjamin Harrison epidemic of influenza B was part of the nation-wide epidemic in the fall and winter of 1945–1946. The authors had an opportunity to study specimens from other stations in the Middle West and found serologic evidence of influenza B in army installations in Indiana, Kentucky, Ohio and Nebraska during the months of November and December.

Although the disease at Fort Harrison was mild and associated with few, if any, complications, the clinical findings indicate that it was similar to the general picture of influenza described by Mote.[5] We are unable to distinguish, on clinical evidence alone, influenza B which we saw in 1945, the influenza A which we saw in 1941 and the syndrome called ARD. These clinical similarities emphasize the need for laboratory studies on acute respiratory disease for accurate diagnosis. Since it appears that widespread epidemics are preceded by scattered outbreaks of influenza in the spring and summer, such laboratory studies would forecast the need for vaccination aimed at general prevention.

Summary. Clinical, epidemiologic and laboratory findings showed that there was an epidemic of influenza B at Fort Harrison, Indiana, during the fall of 1945. In addition to serologically proven cases of influenza, a clinically indistinguishable syndrome referred to as ARD was present.

Influenza B was known to be present in this area in the spring of 1945, and it

is suggested that the virus persisted in the region through sporadic or inapparent cases throughout the summer of 1945.

It is recommended that virologic studies be carried out during the interepidemic periods in order to establish the presence of influenza in a region, and to predict the need for vaccination.

We wish to acknowledge the technical services of Sgt. Glenn Wilson and Miss Beverly Guthner who performed many of the serologic tests, and the coöperation of medical officers at the Station Hospital who graciously showed us patients and the records.

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ENDOCARDITIS DUE TO TYPE B HEMOPHILUS INFLUENZÆ INVOLVING ONLY THE TRICUSPID VALVE

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The following case report merits publication because a review of the literature indicates that no other instance of bacterial endocarditis due to Type B *Hemophilus influenzæ* has been recorded. The case is of further interest because bacterial vegetations involved only the tricuspid valve.

Case Report. U. H. No. 771440. *Present Illness.* V. B., a 17 year old school girl entered the hospital on July 26, 1946, because of a debilitating and febrile illness of unknown etiology. About 3 months previously, she had a gradual onset of weakness, anorexia and increasing fatigability. Shortly thereafter, there was an abrupt onset of sharp pain in the left side of her chest anteriorly, which was associated with chills, fever and drenching sweats. She also had pains in the calves of both legs, and generalized aching of the joints. She was hospitalized elsewhere for 7 weeks, during which time she received penicillin and sulfadiazine. During her stay in the hospital she had 3 episodes of epistaxis. Coincident with this treatment she improved and felt fairly well for 2 weeks after returning home. About this time, the mother of the patient was told that a rough sound over her heart had appeared. She was readmitted to the hospital because of fever, malaise, anorexia, nausea and pain in the right side of the abdomen. She developed pain and swelling over the right ankle. Since the onset of her illness, she had noted some impairment of hearing in the right ear. She was transferred to the University Hospital for further evaluation of her illness. Just prior to entry, giddiness and mild dysuria had appeared. At no time had the patient complained of tender fingers and toes, nor orthopnea and edema. No petechiæ had been noted.

Past History. According to the mother the patient's past life had been characterized by the absence of robust health. At the age of 5 or 6 years she had pains in the calves; from ages 8 to 10 she was said to be more "nervous, jumpy and jerky" than any of her 10 siblings. She had had scarlet fever without known complications, rubella, varicella and mumps. Her heart had not been examined since the age of 8.

Physical Findings. The patient was fairly well developed, pale, and she appeared acutely ill. The temperature was 101° F.; pulse, 120 per minute; respirations, 24 per minute; and blood pressure, 106/70. The pupils and fundi were normal. There was clotted blood in the right ear canal with an intact membranous tympanum. The pharynx appeared normal. The lung fields were clear. The heart was thought to be enlarged 8 cm. to the left of the midsternal line. There was a harsh systolic murmur in the fourth left intercostal space; no diastolic murmur was heard at this time. The rate increased from 120 to 140 in changing from the lying to the sitting position. A protodiastolic gallop rhythm was noted. The liver and spleen were not palpated; both renal areas were tender. Neither petechiæ nor edema were noted. The neurologic examination was within normal limits.

The initial impressions were acute rheumatic endocarditis and renal pain due to sulfadiazine. The latter impression was strengthened by the presence of a sulfadiazine blood level of 2.8 mg. per 100 cc. and sulfonamide crystals in the urine. Therapy with sulfadiazine therapy was discontinued and the crystals were not found in the urine after the first day.

Laboratory Studies. Blood examination disclosed a hemoglobin of 11.8 gm., an erythrocyte count of 3,680,000 and a leukocyte count of 9850 cells per c.mm. The differential count showed 89% neutrophils, 10% lymphocytes and 1% monocytes. Further hematologic studies revealed a hyper-

plastic sternal marrow, and histiocytes and undifferentiated reticular cells in the peripheral blood, some of which contained ingested erythrocytes. On the basis of the latter finding the presence of a bacteremia or possibly subacute bacterial endocarditis was suggested.

The leukocyte count varied from 14,450 to 4800 cells per c.mm. On 3 occasions a 4% eosinophilia was recorded. The sedimentation rate was measured at 40 to 91 mm. in 60 minutes (Westergren). Albumin was present but once in 22 examinations of the urine. Sugar was frequently present from a trace to 1+ quantities; the fasting blood sugar was 76 mg. per 100 cc. of blood. The highest urine specific gravity was 1.026.

Repeated blood cultures remained sterile with the exception of the presence of a coagulase negative staphylococcus on 2 occasions. Microörganisms were absent from smears and cultures of pleural fluid removed during the 2nd week. A spinal fluid examination on the 34th day showed normal findings. The Kline reaction of blood serum was negative. A tuberculin (1–100) test and a skin test with the nucleoprotein fraction of streptococcus remained negative. The antistreptolysin titer was 250 units. Agglutinins for brucella, *P. tularensis*, *E. typhosa* and paratyphosa were absent. The capillary fragility test was negative. The blood urea nitrogen was 7 mg. per 100 cc. at the end of the 1st month. A biopsy of the left deltoid muscle showed normal tissue.

Electrocardiograms revealed a first degree heart block. This finding was constant throughout her hospital stay.

On admission a roentgenogram of the chest showed evidence of a right pleural effusion and pneumonia of the right lower lobe, both of which slowly receded and were followed by similar changes on the left side.

Course. The temperature followed an erratic pattern. During the 1st month her temperature ranged from normal to 101° F., with rises to 103° F. every 3 to 5 days. These intermittent febrile episodes were associated with chills and exacerbations of the chest pain. At the end of a month of observation the temperature rose to 104° and 105° F. daily and continued to do so until 3 days before death when it returned to normal levels. The blood pressure was at no time elevated; the systolic was usually below 100 and the diastolic below 60 mm. of Hg. Additional physical findings appeared, which were a palpable spleen, and a low-pitched diastolic murmur heard to the left of the sternum in the fourth intercostal space. Besides exhibiting febrile episodes, accompanied by chest pain, the patient also complained of pain in the abdomen, flank and legs during the last 2 weeks of life. These areas were tender to palpation, as well as various muscles, tendons and bones, even when examined gently.

Shortly after admission to the hospital the patient was given 50,000 units of penicillin intramuscularly every 2 hours, but therapy with penicillin was discontinued within a week. A month later penicillin was administered again, and she received a total of about 10 million units without apparent benefit. When she was not receiving penicillin, she was given 6 gm. of sodium salicylate daily for 33 days. She also received whole blood transfusions, vitamin preparations, ferrous sulphate and sedatives.

Regardless of the treatment, her course became progressively worse. On the 49th hospital day, bilateral ankle clonus was elicited. She became progressively more delirious and finally comatose. On the 62nd day jaundice was noted. The one minute bilirubin test on the blood serum showed 7.9 mg. % with a total of 11.5 mg. Bile was present in the urine. A cephalin flocculation test gave a 4+ reaction in 48 hours. The liver was not palpable. She died suddenly on the 66th day.

AUTOPSY. (21 hours after death.) *Gross Findings.* The body was that of a 17 year old white female 170 cm. in length, weighing an estimated 105 pounds. She was well developed but poorly nourished. Rigor, hypostasis and minimal cyanosis were present; jaundice was marked. There were 15 small petechiæ over the sternal area.

The *peritoneal cavity* contained 500 cc. of clear amber colored fluid; the right *pleural cavity* contained 30 cc. and the left 15 cc. of a similar fluid; there were 35 cc. of clear fluid in the *pericardial* sac. There were fresh pleural and interlobar adhesions on the right.

The *heart* showed a square milk spot 2 cm. in size over the anterior surface of the right ventricle. The margin of the mitral valve was slightly thickened but was not deformed and did not have vegetations; the chorda tendineæ appeared normal. The valve measured 7 cm. in circumference. The aortic

and pulmonary valves appeared normal. The entire length of the tricuspid valve was occupied by large, yellow, warty vegetations extending a full 18 mm. out from the valve margin. The vegetations extended down the chorda tendineæ and there was one patch on the ventricular endocardium. The auricular endocardium was free of involvement. The heart weighed 275 gm.; no chamber was notably dilated or hypertrophied. The right ventricular wall measured 4 mm. in thickness along the lateral wall and 2.5 mm. at the lower margin. The coronary arteries were normal.

The right *lung* weighed 880 gm., the left 675. There were multiple fine petechiæ over the posterior visceral pleural surfaces of both lungs. There was widespread bilateral pulmonary edema. There were 3 small hemorrhagic areas grossly resembling infarcts (1 in the lower portion of the right upper lobe and 2 in the inferior portion of the left lower lobe). No emboli were seen grossly. Throughout the areas of pulmonary edema there were scattered foci of bronchopneumonia. This was particularly apparent on the left side.

The *spleen* was greatly enlarged, extending well below the costal margin and toward the midline. It weighed 830 gm. No infarcts were identified.

The *liver* weighed 2250 gm. There were no infarcts nor occlusions of the hepatic artery. The liver appeared to be affected by cloudy swelling.

The right *kidney* weighed 100 gm., the left 125. Both capsules stripped easily and the surfaces appeared normal. The lower pole of the right kidney showed an old depressed scar.

The *brain* showed congestion of the vessels.

MICROSCOPIC EXAMINATION. *Heart.* The aortic and pulmonary valves were normal. The mitral valve had prominent blood-vessels and an increase in collagen with fibroblastic proliferation in the free edge of the valve. There was no fibrinoid material. The slight thickening noted grossly and the microscopic changes indicated an old rheumatic infection which had not healed completely and which had not caused serious valve deformity. Sections of the tricuspid valve showed the large thrombus composed of platelet masses, polymorphonuclear cells and scattered gram-positive, pleomorphic organisms seen for the most part as small rods, which were rounded on the ends. There were no microörganisms resembling streptococci or staphylococci. Some areas of the thrombus showed granulation tissue. Underlying the thrombus in the valve itself was considerable fibroblastic proliferation. There were some prominent vessels but no palisade arrangement of cells nor fibrinoid material. The adjacent endocarditis probably accounted for the fibroblasts and dilated vessels; there was no positive microscopic evidence of old or recent rheumatic infection and the conclusion was that the hemophilus infection was the first invasion of this valve. The heart muscle showed a mild diffuse polymorphonuclear myocarditis.

Lung. Most of the sections showed some alveoli filled with erythrocytes or precipitated fluid with the alveolar wall disrupted in some regions. Adjacent to these areas there were thrombosed veins and less frequently thrombosed arteries. Adjacent to these areas small arteries and arterioles were seen in all degrees of thrombotic or embolic occlusion; occasional veins were similarly plugged. The corresponding vessel walls were infiltrated with polymorphonuclear cells, sufficient in some instances to be termed an arteritis. The *pleura* was thickened.

Kidney. The glomeruli were enlarged and showed considerable endothelial proliferation but blood cells could be seen in the capillaries. The tubules and vessels appeared normal. There were many small collections of lymphocytes particularly near the glomeruli. The conclusion was subclinical acute glomerulonephritis. The sections through the old scar showed complete hyalinization of many glomeruli.

Bladder: There was a mild cystitis.

Liver: There was a very slight fatty metamorphosis in the cells adjacent to the central veins.

Spleen: The red pulp was engorged with erythrocytes. There was an increase in the number of polymorphonuclear cells in the pulp and particularly in the sinusoids. The conclusion was acute splenitis.

Adrenal: There were some collections of lymphocytes in the medulla.

Pancreas: Sections showed nothing remarkable.

Brain: Sections of the brain showed scattered acute inflammatory lesions. In some regions there was a number of neutrophils

throughout the leptomeninges. The conclusion was early suppurative encephalitis.

BACTERIOLOGIC STUDIES. At autopsy blood was withdrawn from the right ventricle under sterile precautions. The heart was opened aseptically, smears were prepared from the vegetations, and portions of the vegetations were placed in tryptose phosphate broth. Gram stains of the smears revealed small, gram-negative rods with rounded ends. Similarly staining organisms were obtained from the cultures of heart's blood and from the vegetations. Growth of the organisms took place only in presence of "X" and "V" factors. The organisms failed to grow on the surface of blood agar. However, growth was supported on freshly prepared chocolate agar plates. Growth also took place on blood agar plates adjacent to colonies of coagulase-positive staphylococcus, but without hemolysis around the small, opaque colonies of *H. influenzæ*. Organisms from young cultures in broth revealed the presence of capsular swelling when mixed with Type B *H. influenzæ* rabbit antiserum. This specific Quellung phenomenon was corroborated in 2 different laboratories.

Although the Gram-Weigert tissue stain showed the organisms in sections of the vegetations to be gram-positive, stained preparations of smears of the vegetations and of the organisms cultured from the heart's blood were consistently gram negative. The dissimilarity between the 2 staining techniques has been noted with other gram-negative organisms.[11]

Comment. Influenza bacilli associated with human disease have been divided into 2 main groups, namely, *H. influenzæ* and *H. parainfluenzæ*. The former requires the so-called "X" and "V" factors for growth, whereas the growth of the latter is supported by only the "V" factor. Furthermore, as Pittman[8] and Platt[9] have shown, smooth, encapsulated strains of *H. influenzæ* may be divided into several types with specific antisera. In a review of the reported cases of influenzal endocarditis, Craven, Poston and Orgain[5] have accepted 36 cases, including 2 of their own, as being due to influenza bacilli. But in this group there was not one proved case caused by *H. influenzæ*. More recently, Rose[10] reported the clinical and pathologic findings of the first authentic case of bacterial endocarditis due to *H. influenzæ*. The causative organism was Type A *H. influenzæ*.

In the present case, a pure culture of *H. influenzæ* was isolated from the vegetations on the tricuspid valve. Growth of this organism took place only in the presence of "X" and "V" factors, and when studied in 2 different laboratories, was found to be *H. influenzæ*, Type B. Repeated cultures of venous blood during life remained sterile. There were no demonstrable embolic phenomena while the patient was under observation. The sterile cultures and absent peripheral emboli may be accounted for by the fact that localization of the lesion was on the right side of the heart, and the lungs filtered out the organisms from the blood. It is unfortunate that the bacilli were not isolated from the blood stream during life, since it has been demonstrated that strains of Type B *H. influenzæ* are sensitive to the antibacterial action of streptomycin.[2] Cultures of the strain obtained at postmortem were lost before their *in vitro* sensitivity to streptomycin could be determined. It is of interest that Type B *H. influenzæ* is the most frequent cause of meningitis in infants under 12 months of age at the University of Minnesota Hospitals. However, this organism rarely causes serious disease in adults. Alexander,[1] who has had an extensive experience with infections caused by this species of influenza, has never encountered it as a cause of bacterial endocarditis.

Kresky[6] has reported a case of a 3 year old girl who died of suppurative pericarditis due to Type B *H. influenzæ*. At autopsy, the endocardium and surfaces of the valves appeared normal. He described 5 other cases collected from the literature, 3 with meningitis. Postmortem examination was carried out in 2 of the 5 cases and no valvular disease was found.

Another pertinent feature of the findings in the present case was the localization of the bacterial vegetations on only the tricuspid valve. Blumer,[3] in a review

of 146 cases of subacute bacterial endocarditis which came to autopsy, stated that the tricuspid valve was the only valve involved in 3 cases (2%). Middleton and Burke[7] found 1 out of 49 cases at the Wisconsin General Hospital with involvement of the tricuspid valve only (2%). In the material studied in the Department of Pathology at University of Minnesota Medical School, Clawson[4] observed localization of vegetations on the tricuspid valve alone in 7 of 363 cases of subacute bacterial endocarditis (1.92%).

There were no features in this patient's illness which, on an etiologic basis, would serve to distinguish the clinical course from that of other cases of subacute bacterial endocarditis due to *H. parainfluenzæ*. This is in agreement with the conclusions of Rose[10] with respect to his case of Type A *H. influenzæ*. The atypical clinical course may be ascribed in part to the localization of the bacilli on the tricuspid valve.

Summary. 1. The clinical and pathologic findings are described for a case of subacute bacterial endocarditis due to Type B *H. influenzæ*. As far as can be determined, this is the first proved instance of bacterial endocarditis caused by this species of influenzæ.

2. The bacterial vegetations were localized on only the tricuspid valve.

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STREPTOMYCIN THERAPY OF TULAREMIA IN U. S. ARMY HOSPITALS

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Heilman[5] first reported in 1944 that streptomycin exerts a strong *in vitro* action on *Pasteurella tularense* and is capable of curing the experimentally produced disease. This action was subsequently confirmed by us.[8] The first report of its clinical use in tularemia was by Foshay,[3] who reported that after its administration[6] patients with infection of the ulceroglandular type all showed subjective improvement, regression of lymphadenitis, and remission of temperature. Other reports were to the same effect.[1,2,4,8] The National Research Council's most recent report[7] on streptomycin in the treatment of infections included 67 cases of tularemia with 63 recoveries, on the basis of which the following statement was made: "It can be stated with confidence that streptomycin is an extremely effective agent in tularemia and that it is by far the best therapeutic agent available for the treatment of this disease. Early diagnosis and treatment by intramuscular injection for 5 to 7 days with an average amount of 1 gm. daily should be used in all patients. In the pulmonary and pleural forms with continuous fever without localizing signs, it is desirable to give 2 gm. daily for 7 days or longer until the disease is under control."

Present experience in the Army Streptomycin Study program covers 10 cases of tularemia, 1 of the typhoidal and the others of the glandular type. Pneumonia was a complication in 3 cases, in 1 of which it was associated with nephritis. The patients, who were all adult males, acquired the infection in the South or Southwest of the United States. Two patients had had recent contact with wild rabbits and 4 presented tick bites at the site of the local lesion. In the 2 remaining cases the history of contact was obscure. All patients had, or later developed, specific agglutinins in high titer, but the causative agent was isolated from only 2 patients.

Streptomycin was administered to all patients intramuscularly at intervals of 3 or 4 hours in daily doses of 1 to 3 gm. for periods of 7 to 14 days. Recovery was smooth in all cases, without relapses or complications.

Report of Cases. Case 1. *Typhoidal type.* A white male, 32 years of age, who had killed and dressed wild rabbits a week earlier, suddenly developed headache, generalized aching, chills, fever and stiff neck. The patient's brother-in-law who also helped dress the same rabbits was admitted to another hospital because of an ulcer on his finger and a diagnosis of "rabbit fever." On admission the temperature was 104.5° F. with extreme nuchal rigidity, suggestive Babinski and Kernig signs. No localized swelling or tenderness was evident on examination. The abdomen, heart, and lungs were clinically negative. The spinal fluid was negative. The white blood count was 11,700 (77% polys with 10% stab cells). The admission chest film was negative. On the basis of the above findings, a tentative diagnosis of tularemia, typhoidal type, was made. The day after he was hospitalized, which was the 8th day of illness, blood serum agglutinins for *P. tularense* were positive in a dilution of 1:40. Roentgenologic examination confirmed the presence of a right lower lobar pneumonia, but no causal organism could be grown from the sputum.

Streptomycin was administered in doses of 0.125 gm. intramuscularly every 3 hours. The temperature promptly fell from 105° F. to normal, the fall being followed by a secondary rise to 100° F. At the end of 48 hours, because of temporary exhaustion of the supply, the drug was discontinued for

12 hours. The temperature promptly rose to 105° F. It was then resumed for 5 days a total dosage of 6 gm. being given; 36 hours after resumption the temperature fell and remained under 100° F. Residual fever subsided by lysis by the 7th day and the pneumonic process cleared completely by the 12th day. No clinical relapse occurred. In the meantime the blood serum agglutinins had increased steadily until a titer of 1:2560 was maintained.

pneumonia was confirmed by roentgenologic examination. Blood and sputum cultures were non-contributory. Urine showed a moderate albuminuria and culture grew *P. tularense*. The blood serum agglutination titer was 1:1480.

Streptomycin was administered intramuscularly in doses of 0.2 gm. over a 14 day period at 4 hour intervals. A total of 15 gm. was given. The response was slow but progressive. The patient became afebrile on

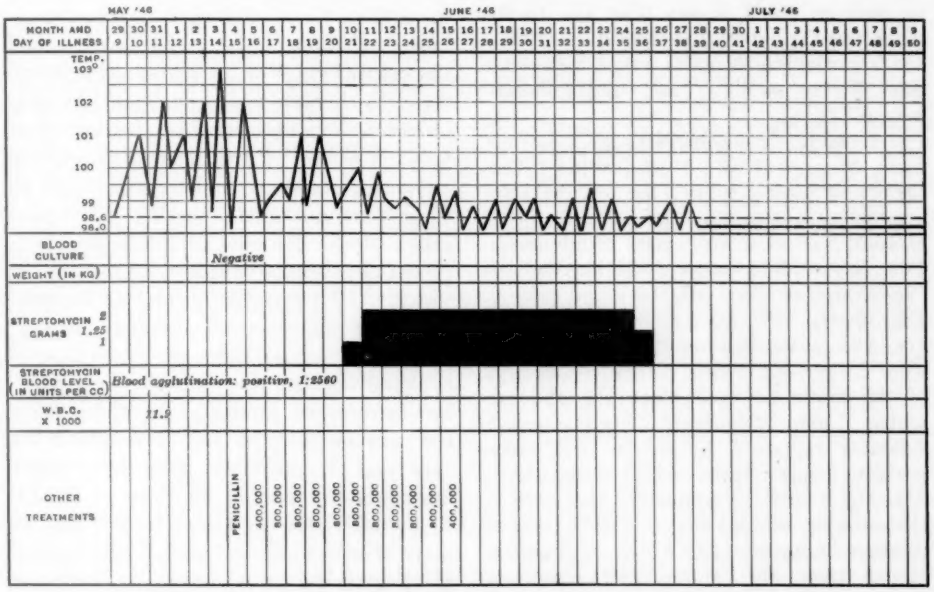

FIG. 1.—Case 3. Ulceroglandular tularemia, complicated by pneumonia.

CASE 2. *Ulceroglandular type.* A white male, 23 years of age, developed a lesion on the back of the left hand 4 days after hunting rabbits. He developed fever, chills and generalized aching and pain localized in lower back region; more on the left side. A local physician administered 25 doses of penicillin without benefit. He continued with severe generalized muscular pains of arms, legs, back and neck, and began to notice a cough and some pain in his left chest. When he was hospitalized, on the 32nd day of illness, the epitrochlear and axillary lymph nodes were enlarged and tender. The lesion on the back of the left hand was ulcerated and presented a black eschar; it was 2 cm. in diameter. On the left thumb was a smaller lesion of the same kind. Clinical evidence of bilateral bronchothe 35th day of illness and the urine became completely free of albumin 1 month later. In the meantime the primary ulcer had healed slowly and the lung had cleared.

CASE 3. *Ulceroglandular type.* The patient, a white soldier, 23 years of age, developed ulceration of the forehead in the region recently traumatized by a sharp blow, with fever and enlargement of the anterior cervical lymph nodes, 3 weeks before admission. When first seen in the hospital, the physical examination was negative except for a small ulcer of the forehead about 2 cm. in diameter and 0.5 cm. deep, and enlarged lymph nodes of the anterior cervical chain. The blood serum agglutination was positive for *P. tularense* in a dilution of 1:2560.

Streptomycin therapy was begun by the intramuscular route in doses of 0.25 gm.

every 3 hours and was continued for 15 days. A total of 30 gm. was given. The ulcer improved rapidly, and was healed in 7 days. The cervical lymph nodes became fluctuant and required incision and drainage. Cultures on cystine media of material taken from lymph nodes were negative, as were cultures of the ulcer taken before streptomycin was begun. The illness was complicated by a right lower lobar pneumonia, presumably of tularemic origin, since no other etiologic organism could be grown. Fever subsided by lysis on the 35th day (Fig. 1). In the meantime the pneumonia cleared, and drainage from the lymph nodes ceased with recession of the swelling, and uncomplicated wound healing.

CASE 4. *Oculoglandular type.* A white male, 26 years of age, was admitted with a history of having rubbed the left eye after scratching the site of a tick bite on the lower extemity, about a week prior to admission. Four days before entering the hospital the eye became swollen, red, itchy and painful. Examination revealed a swollen, tender, left eye with a marked conjunctivitis. There were 2 opposing ulcers of the conjunctiva of the lower lid each measuring approximately 3 mm. in diameter. There was considerable marginal hyperemia and some purulent exudate in the vicinity of the ulcers. A string of small, lymph nodes presented in the anterior cervical chain, and the largest measured approximately 1 cm. in diameter. Smear from the conjunctival ulceration showed small gram-negative rod-like organisms morphologically resembling *P. tularense.* On admission the temperature was 103° F. Blood serum agglutination for *P. tularense:* day of admission, negative; at the conclusion of therapy, positive, 1:80; 1 week after cessation of therapy, negative. Urinalysis, complete blood count and blood serologic tests were non-contributory. A diagnosis of oculoglandular tularemia was made. The patient was given streptomycin, 0.4 gm. intramuscularly every 3 hours for 12 days, and in addition, topical applications of streptomycin, in sterile isotonic saline, 3 mg. per cc. 4 to 8 drops 4 times a day. The acute inflammatory process subsided rapidly. On the 9th day of treatment the eye appeared normal, the ulcerations were healed, the vision of the left eye was 20/30. At the time of discharge, 1 week later, recheck of the vision showed 20/20 readings.

Comment. In Case 1 the dramatic, immediate response to streptomycin was not maintained because lack of supply caused an interruption in continuity of administration of the drug. Cure was effected when a second course was given, and the drug assuredly influenced the result. In Case 2 streptomycin therapy, while not dramatic in effect, undoubtedly played a rôle in the patient's recovery; the severity of his illness would ordinarily have been associated with a grave prognosis. In Case 3 the patient had passed the critical stage of his illness when streptomycin therapy was begun, and the only objective evidence of therapeutic effect was the healing of the ulcer focus and the recession of the lymphadenopathy. In Case 4 streptomycin therapy effected a rapid cure. The conjunctivitis and associated ulcers healed within 9 days, and the vision in this eye was normal at the conclusion of the course of therapy.

The remaining 6 cases are not presented in detail because they contain no particular features of interest. In these cases the disease was of the ulceroglandular type and diagnosis was made by positive agglutination tests in dilutions of 1:1280 to 1:5120. Each patient had 7 gm. or more of streptomycin over a 7 day period. Healing of the initial lesion, in each case in the groin, was slow but progressive, and regression of the associated lymphadenopathy was also progressive. In 3 instances suppuration of the lymph nodes was extensive enough to require aspirations. With streptomycin therapy wound healing will follow surgery.

The combined experience of all observers indicates that streptomycin is the most effective drug presently available for the treatment of tularemia. Given in doses of 1 to 3 gm. daily it causes remission of the local and systemic manifestations of the disease. A dosage in the amount of 2 gm. daily appears preferable and is recommended. Duration of treatment varies from 7 to 14 days, depending upon the type and severity of the infection. In the later stages of the ulcero-glandular

form of the disease, the rôle of streptomycin therapy is less significant, since (1) spontaneous cures are known to occur, and (2) the observed changes in our series of cases were slow.

Summary and Conclusions. 1. Streptomycin is the most effective drug available for the treatment of tularemia. Employed in doses of 1 to 3 gm. a day, the antibiotic produces remission of the local and systemic manifestations of the disease. A 2 gm. a day dosage schedule appears preferable and is recommended. Duration of treatment varies from 7 to 14 days, depending upon the type and severity of the infection.

2. Experiences with 10 cases of tularemia treated with streptomycin in U. S. Army hospitals are presented.

3. Accidentally or deliberatey incised or excised buboes of tularemia heal with adequate streptomycin therapy.

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FURTHER OBSERVATIONS ON POLIOMYELITIS IN PREGNANCY

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In 1945 Fox and Sennett[3] summarized the literature and analyzed the clinical data showing increased susceptibility to poliomyelitis. They recognized a total of 85 cases up to and including the epidemic of 1943. It is apparent that not all cases of poliomyelitis in pregnant women were recorded in the medical literature or included in the paper by Fox and Sennett.[3] Since it seems important to establish thoroughly whether any true relationship exists between poliomyelitis and the pregnant state, we are presenting additional information in this paper.

Table 1.—Data on 14 Cases in 1945 and 1946

Patient	Age	Duration of pregnancy	Convalescence	Result of pregnancy
		1945		
1. Mrs. N. McF.	35	1½ mos. pregnant	Slight stiffness of neck and back persisted	Expelled blood and products of conception on 3rd to 5th hosp. day
2. Mrs. J. O'C.	19	2 " "	Muscle weakness persisted	Miscarriage ? mo.
3. Mrs. F. L.	38	3 " "	Recovery of muscle spasm and paralysis	Delivered normal baby
4. Mrs. A. K.	25	5 " "	Paralysis of lower limbs	Pt. delivered by Cesarean section but baby died due to Rh factor
5. Mrs. L. K.	30	8½ " "	Died 9 days postpartum	Delivered normal 6 lb. 1 oz. boy
6. Mrs. M. R.	27	5 days postpartum	Died 12 days postpartum	Normal baby
		1946		
1. Mrs. W. L.	21	1 mo. pregnant	Marked paralysis (in Emerson respirator at time)	Aborted 1 mo.
2. Mrs. C. E.	23	3 mos. pregnant	Complete recovery	Miscarriage at 3 mos.
3. Mrs. E. B.	31	3½ " "	Recovery of all muscles	Subsequently delivered normal baby
4. Mrs. D. S.	26	3½ " "	Recovery of all symptoms	Subsequently delivered normal baby
5. Mrs. J. E.	27	5 " "	Residual paresis	Miscarriage 3½ mos.
6. Mrs. M. A.	27	6 " "	Complete recovery	Normal delivery
7. Mrs. E. T.	22	7½ " "	Weakness of muscles involved; persisted with little change	Delivered normal baby
8. Mrs. N. P.	23	14 days postpartum	Slight spasm of neck with pain in back muscle and pain of quadriceps	Normal baby

Data from the 1945 and 1946 epidemics are listed in Table 1. In the 1945 epidemic, 10 married women were admitted to the South View Isolation Hospital, 6 (60%) of whom were pregnant. These patients were in various stages of pregnancy: 3 in the first trimester, 1 in the second, 1 in the third and 1 patient who delivered only 5 days previous to the onset of the disease. In the 1946 epidemic, 14 married women were admitted to the Hospital. Of these, 8 (57.1%) were pregnant. Two patients were in the first trimester, 4 in the second, and 1 in the third. One patient had delivered a normal child 14 days previously.

Thus there seems to be no preponderance of patients in any one of the pregnancy trimesters. Waaler[16] also had found no time relationships as far as inci-

dence is concerned, but he did cite the fact that "the prognosis for mothers contracting poliomyelitis in the last months of pregnancy is bad," since 8 of his 33 patients died in the last two trimesters. Of our 24 cases, 2 died in the last two trimesters. Aycock[1] states that there are fewer cases in the first 2 months of pregnancy, and also concludes from his data "that there is a tendency for the disease to occur in the first trimester in those who are carrying a female fetus." Certainly, additional data would be welcome from further sources to support this interesting observation.

In attempting to summarize the total number of cases of pregnancy complicating poliomyelitis, or of poliomyelitis complicating pregnancy, one is struck by the relative paucity of recorded literature on the subject. The discussion regarding intrauterine poliomyelitis has brought to light several instances of pregnancy complicated by poliomyelitis. While the majority of the authors were primarily concerned as to whether poliomyelitis in the mother has an effect on the fetus, all the cases cited in these reports can be included in the present tabulation. These papers, however, furnish no comparative data as to the incidence of the disease in gravid *versus* non-gravid women, which is a very important consideration. Harmon and Hoyne[6] cite 2 women, aged 30 and 32 years respectively, who were in the 6th and 8th months of gestation. Wakefield[17] reported 1 woman 18 years of age who developed poliomyelitis during the 12th week of pregnancy. Subsequently, she delivered uneventfully a normal child at $8\frac{1}{2}$ months. The report by Waaler,[16] on various aspects of the problem, cites 33 cases of poliomyelitis in women in different stages of pregnancy. He also notes that in the Bergen, Norway, epidemic of 1941, the Epidemiologic Department of the Haukeland Hospital had 23 women, 7 of whom were pregnant. Netteblad[12] quoted 6 cases out of 42 adult women. Jacobsen[9] observed 7 pregnant women with poliomyelitis and Palmstierna[13] had 2 cases of poliomyelitis in mother and new-born infant. Hürny[8] mentioned 2 cases and Schultze,[15] Zimmermann,[18] Guttman,[4] Ruhl,[14] Hansen,[5] and Morrow and Luria[11] mentioned 1 case each. Waaler[16] claims to have succeeded in finding only 25 cases of poliomyelitis in pregnant women in the literature. He was obviously handicapped in his search for the American literature was evidently unavailable to him. In our judgment, the literature shows a total of 71 cases of pregnancy with poliomyelitis. An acurate diagnosis is essential in any consideration of the subject. Without complete verification, cases not poliomyelitis could pass as such.

We wish to refer now to an interesting illustrative case.

CASE 1.—A 27 year old white female was admitted to the South View Isolation Hospital, having had a normal spontaneous delivery of a live and healthy baby girl. During her labor she suddenly developed dizziness and presented a right hemiplegia with inactive right diaphragm, and a flaccid paralysis of the right arm and leg. She became increasingly worse and was admitted to the Hospital as a poliomyelitis suspect 4 days later.

Physical examination revealed a well-developed and well-nourished white female who had a paralyzed right arm and leg, pain and tenderness in the right shoulder and arm, absent knee jerks bilaterally, and marked weakness of the left arm and left leg. Her respirations were labored and she was unable to void. A catherized specimen of urine was cloudy and contained 4+ albumin and numerous pus cells. Spinal puncture released fluid which contained 150 RBC per c.mm. and 15 WBC per c.mm. Two days later the spinal fluid contained 274 RBC per c.mm. and 2 WBC per c.mm. Her temperature remained elevated, varying between 99.6° and 105° F. Examination on September 12 revealed a completed flaccid paralysis of the right arm and right leg, right sternocleidomastoid, and right diaphragm. She was barely able to move the fingers of her left hand and the toes of her left foot. The left diaphragm was active, but the right side of the chest was entirely

inactive. Cough reflex was present but weak, and her ability to swallow at this time appeared to be unimpaired. The bladder did not function and required catheterization. Two days later she developed increasing difficulty in swallowing and did not respond to questions. The mucus collecting in her pharynx had to be aspirated frequently and she continued a progressively downward course, finally becoming moribund. Death occurred on Sept. 16, 1945.

Necropsy. The following significant lesions were found in the brain and spinal cord. The medulla showed a gray-pink discoloration of the posterior one-third of the floor of the fourth ventricle; the right side was frankly hemorrhagic. The serial sections throughout the medulla and cervical cord showed that the hemorrhage formed a continuous columnar structure extending well into the upper portion of the cervical cord. The hemorrhagic area was located in the right side of the cord and involved primarily the right anterior column. Microscopic examination revealed an irregular area of hemorrhage and softening in the right ventral area. The hemorrhage destroyed the tissues in this area while the surrounding zone was vacuolated, congested, and exhibited neuron degeneration. The anterior horn cells throughout the lumbar and thoracic cord were without significant change. The postmortem conclusions were that this was a case of hematomyelia complicating labor.

The interesting point about this case is the ease with which it could be misdiagnosed as a case of acute anterior poliomyelitis, were it not for the necropsy and spinal fluid findings.

The case cited above may be compared to one of poliomyelitis.

Case 2. A 30 year old woman, pregnant 8½ months, entered South View Isolation Hospital on Nov. 11, 1945, with complaints of pain in the back of the neck and along the back of the thighs and lower back. Temperature on admission was 98.8° F., pulse 132, respirations 26. Reflexes were 0 to 1+ with flaccid paralysis of both lower extremities, flaccid paralysis of the right arm, and weakness of the left arm. This patient was able to swallow without too much difficulty but developed slight occasional twitching at the left angle of the mouth on the 2nd hospital day. On the 3rd day, she gave birth to a 6 pound 1 ounce boy who was and who has remained normal in every respect. The patient's left arm became progressively weaker and by the 6th hospital day she had paraplegia with increased bulbar involvement. She could protrude her tongue only slightly, could open her mouth about 1 inch, and had profound weakness of the facial muscles, especially on the left side. On the evening of the 8th hospital day, the patient had increasing difficulty swallowing as well as a rise in temperature to 100.2° F. The course was unchanged until the 12th hospital day when she had very shallow respirations, a rise in temperature, and a fall in blood pressure. The cough reflex disappeared and the patient died that evening.

Laboratory findings showed the spinal fluid clear on admission: 20 cells with 100% lymphocytes. The urinalysis was negative throughout the hospital stay until the day of death when it showed a 4+ albumin, 15 WBC per low-power field and 10 RBC, and an occasional cast.

Treatment included hot packs to the affected limbs and symptomatic medication.

Autopsy. Pertinent findings were limited mainly to the brain and spinal cord. These confirmed the clinical diagnosis of poliomyelitis. A focal hemorrhage of the substantia nigra, minute hemorrhages in the cervical cord, pulmonary congestion, basal atelectasis, and an area of myocardial degeneration were also noted.

These 2 cases are presented for comparative purposes to point out the fallacy of regarding a case of paralysis as poliomyelitis merely because it occurs during the epidemic season, when no other cause can be ascertained at the moment.

It is of some interest to note that both grossly and microscopically this case exhibited multiple hemorrhages. So far as we can determine, this occurrence has not been noted in the pathologic changes of poliomyelitis.

Discussion. It seems from our data, as from several reports on the subject, that the pregnant woman is apparently more susceptible to the poliomyelitis virus than the non-pregnant woman. The previous paper by Fox and Sennett[3] cited several reports in the literature which supported

the thesis that the endocrine glands influence susceptibility or resistance in some way as yet not fully understood. Numerous references can be made to glandular changes which occur in pregnancy, and, as pregnancy progresses, to the effect of the fetal ductless glands on the maternal metabolism; but more specific citations can be made. The theory that the endocrine glands can influence susceptibility to poliomyelitis receives support from Jungeblut and Engle,[10] who believe that immunity in this disease is dependent upon physique and physiologic mechanisms such as menstruation and pregnancy. However, their work, indicating that the immune body content of the sera varied with the menstrual cycle, has been opposed by the more extensive studies of Hudson, Lennethe and King.[7] Jungeblut and Engle[10] found that after adrenalectomy the sera of certain monkeys failed to neutralize the virus. After treatment with cortical hormone, the neutralizing power returned. Adrenalectomy caused the disappearance of the natural poliomyelitis antibody, but the antibody present in animals recovered from the infection did not disappear. For such cases, Aycock[2] introduced the term "autarcesis," the power to resist infection. This quality is inherent in the normal physiologic function of the body. While he admits that immunity following contact with the virus is important, he stresses the rôle of normally changing physiologic imbalance in causing increased susceptibility to infection. The multiple physiologic changes occurring in pregnancy make it seem not unlikely that differences in susceptibility are encountered between the gravid and non-gravid state, which make the gravid patient more susceptible.

Several groups of workers have attempted to determine whether poliomyelitis runs an unusually fatal course during pregnancy, but the evidence cannot be regarded as conclusive. Others have presented evidence that the prognosis is bad for mothers contracting poliomyelitis in the last trimester. This issue also cannot be determined with any finality when we take into consideration that viruses with different characteristics make their appearance during one epidemic and in various parts of the country. The variations from year to year and variations in virulence of the virus are only a few considerations to be kept in mind in a critical evaluation of this matter.

Summary and Conclusions. 1. The total number of recorded instances in which pregnancy complicated poliomyelitis or poliomyelitis complicated pregnancy is well over 175.

2. Data from the 1945 and 1946 epidemics indicate that of 24 married women admitted to the South View Isolation Hospital with a diagnosis of poliomyelitis, 14 were pregnant.

3. The incidence of poliomyelitis appears to be greater in pregnant than in non-pregnant women, though it has not been feasible to confirm our data by statistical methods.

4. One case of hematomyelia is cited which clinically simulated poliomyelitis.

5. Influence of the glandular changes of pregnancy which affect the physiologic balance of the patient and, therefore, susceptibility to poliomyelitis, is offered as a possible explanation for the apparently greater incidence in pregnant women.

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PA-PIN (TRANSIENT PARALYSIS) COMPLICATING ASIATIC CHOLERA

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One of the authors (Huang[7]) reported 12 cases of Pa-Pin, or transient paralysis, simulating familial periodic paralysis. All of these cases showed a uniform clinical picture identical with that of familial periodic paralysis except for 2 points: (1) absence of family history and (2) frequency of the disease in certain salt-producing areas, where the salt was proved to contain high percentage of barium chloride (as high as 25.69% has been recorded).

Du and Dung[5] reproduced a similar symptom-complex in dogs by oral or intraperitoneal administration of pure barium chloride, and believed barium poisoning to be the cause of the transient paralysis.

One of the authors (Huang[8]) was able to produce similar flaccid paralysis of legs of rabbits by intravenous administration of pure barium chloride, but was not able to abolish the paralysis by intravenous application of potassium as in the human cases. Chow[3] repeated it on dogs with the same result.

Chang and Loo[2] reported a case of poisoning with barium due to ingestion of pure barium chloride by mistake. Not only the symptoms and signs were identical with those of Pa-Pin, reported by Huang, and those of familial periodic paralysis, but also the response to administration of potassium was identical.

Except for Huang's failure in using potassium to relieve paralysis caused by barium in rabbits and Chow's similar experience in dogs, all of the evidence on hand speaks for barium chloride as the cause of the fairly common disease, Pa-Pin, in Szechuan Province. The mechanism of production of flaccid paralysis by barium chloride is not known yet. The cases we are reporting may contribute something to the understanding of the metabolism of barium in the human body and the pathogenesis of paralysis.

Case Reports. The authors met 11 cases of the same transient paralysis among 1620 cases of Asiatic cholera admitted to the Provincial Institute during an epidemic in the summer of 1945. All of the cases developed paralysis immediately after recovery from cholera and all responded to treatment with potassium. The diet given in the Institute during the epidemic was absolutely devoid of free salt and no food from outside was allowed. Different samples of sodium chloride used for intravenous infusion were analyzed by Professor Chow* and found to contain no trace of barium. The details of the cases are presented in Table 1 in simplified form.

Discussion. Aitken, Allot, Castleden and Walker[1] found that, in cases of familial periodic paralysis, both serum potassium and urine potassium were reduced during an attack, and serum potassium returned to normal level and urine potassium was increased above normal after an attack. Unfortunately, determination of serum potassium was not made in the cases of transient paralysis, owing to the lack of facilities for accurate analysis under wartime conditions in China. Judging from the clinical features and good response to potassium, the pathogenesis of paralysis should be the same as that of familial periodic paralysis. If so, it is natural to think that barium exerts its action by disturbing potassium metabolism. Naturally, the question arises: whether familial periodic paralysis is also due to barium poisoning or whether barium poisoning is only one of the causes for disturbed potassium metabolism. Feng[6] showed that

* Professor Chow used the colorimetric method as described in his article (Chow, C., and Chin, Y. G. Chinese Med. J., 61, 113, 1943).

TABLE 1.—DATA OF 11 CASES OF PA-PIN*

Case No.	Age	Sex	Duration of disease on admission hours	Main symptoms and signs of cholera: Vomiting	Diarrhea	Anuria	Muscular cramp	Hoarseness	Dehydration	Total amount of normal saline given intravenously (liters)	Appearance of paralysis (time): Day of admission	Day of recovery	Differential blood counts (shortly after onset of paralysis): Red blood cells	Leukocytes	Neutrophils	Lymphocytes	Treatment (total amount of KCl given intravenously)	Course
1	41	M	20	++	+++	Pres.	Pres.	Abs.	Marked	11	5	1		Not done			2% sol. 415 cc. in 3 doses	Dramatically impr. after KCl injection; compl. recov. in 24 hrs.
2	38	M	10	+++	+++	Pres.	Pres.	Abs.	Marked	12	7	2		Not done			2% sol. 550 cc. in 2 doses	Dramatically impr. after KCl; compl. recov. in 20 hrs.
3	39	F	24	++	+++	Abs.	Pres.	Abs.	Marked	16	6	2		Not done			3% sol. 450 cc. in 2 doses	Markedly impr. after KCl; compl. recov. in 3 days
4	30	F	12	++	+++	Pres.	Pres.	Abs.	Marked	19	5	1		Not done			3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 10 hrs.
5	60	M	24	++	++	Abs.	Abs.	Abs.	Marked	9	3	1		Not done			3% sol. 100 cc. in 1 dose	Sudden death after 100 cc. of 3% KCl
6	16	M	12	++	++	Abs.	Abs.	Abs.	Mod.	15	6	2	5.07	12.0	83	17	3% sol. 250 cc. in 1 dose	Mod. impr. after KCl; compl. recov. in 30 hrs.
7	70	M	20	+	++	Pres.	Abs.	Abs.	Mod.	20	5	1	4.30	12.0	91	9	Refused treatment	Disch. against advice; no further information
8	30	F	10	++	++	Abs.	Abs.	Abs.	Mod.	2	2	1	3.96	10.3	91	10	After 100 cc. of 3% sol. patient refused treatment because of pain	Mod. impr. after KCl; compl. recov. in 3 days
9	19	M	48	++	+++	Abs.	Pres.	Abs.	Mod.	9	4	1	5.79	20.8	83	17	3% sol. 500 cc. in 2 doses	Mod. impr. after KCl; compl. recov. in 2 days
10	25	M	20	+	+++	Abs.	Pres.	Abs.	Mod.	15	6	1	5.38	11.4	89	11	3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 3 hrs.
11	55	M	20	++	+++	Pres.	Pres.	Pres.	Mod.	23	9	2	3.76	21.8	95	5	3% sol. 250 cc. in 1 dose	Dramatically impr. after KCl; compl. recov. in 3 hrs.

* All patients were Chinese. None gave history of previous transient paralytic attack. After paralysis appeared all patients showed complete flaccid paralysis of neck and extremities; tendon reflexes and muscular tonicity lost; no sensory disturbance; heart action slow and weak, except in Case 2 where heart action was normal.
Food taken during hospitalization consisted of soy bean milk rice water and powdered arrowroot in all cases. No extra food from outside.

barium chloride bears a striking resemblance to eserine in its action on the motor nerve endings of the frog which is just the opposite to our clinical experience. Certainly it requires a good deal of further study to reconcile the apparent contradiction.

No textbooks of medicine[3,10,11] have ever mentioned Pa-Pin or transient paralysis as a complication of Asiatic cholera. This implies that some additional factor must be at play to give rise to such a manifestation. The fact that it displays an identical clinical picture with that occurring simultaneously speaks strongly for a common causation, and its late onset at the time of recovery from gastro-intestinal symptoms after several days' salt-free diet, with no drugs, except non-barium containing saline infusions, would apparently exclude barium as the responsible factor. However, Kunowski[9] has demonstrated barium in human bone and it would not be illogical to ask whether dehydration and acidosis might not mobilize the deposited barium from bones to cause acute manifestations as in cases of chronic lead poisoning. Dehydration in ourcases may have another effect in precipitating symptoms, as Wiley and Wiley[12] have shown that in marked dehydration (5% of body weight) plasma electrolytes (NaCl) and later KCl from the tissue are sacrificed. The marked dehydration here probably has a 2-fold effect upon the potassium metabolism: (1) mobilizing barium to disturb potassium equilibrium, (2) causing loss of potassium from tissue. The two effects together precipitate the clinical symptoms.

Summary. 1. Pa-Pin or transient paralysis in Szechuan, a disease showing an identical clinical symptom complex with familial periodic paralysis and most likely caused by ingestion of barium-contaminated salt, is reviewed.

2. Eleven such cases complicating Asiatic cholera are reported. Asiatic cholera as a cause of Pa-Pin has apparently not been previously reported.

3. The mechanism of paralysis production is discussed.

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and muscular tonicity lost; no sensory disturbance, heart sounds rice water and powdered arrowroot in all cases. No
Food taken during hospitalization consisted of soy bean milk

THE RELATIVE TOXICITY OF ATROPINE AND NOVATRINE IN MAN

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In the search for a drug possessing an action similar to that of atropine on the autonomic nervous system but which, nevertheless, would be free of its toxic effects, novatrine* was introduced into clinical medicine.[2] Quigley,[4] using unanesthetized dogs, found the dosage ratio of novatrine and atropine for comparable inhibition of gastric motility to be approximately 1.5:1, while the ratio for the colon was approximately 6:1. The same author[5] also noted inhibition of gastric motility by novatrine in normal men. More recently Martin and Batterman[3] found novatrine to be suitable for reducing the tone and motility of the gastrointestinal tract during abdominal surgery under various anesthetics. Batterman and Rose[1] studied the influence of simultaneous aluminum hydroxide therapy on the absorption of novatrine using visual disturbances and dryness of the mucous membranes as evidence of absorption. Their results indicated that the aluminum hydroxide did not affect absorption and that doses of 60 to 150 mg. of novatrine were necessary to cause mild to marked toxic effects. At the time the present investigation was undertaken, there had not been any carefully controlled study of the toxic manifestation of novatrine as compared to those of atropine, nor has any such comparison appeared since. The purpose of the present investigation was to make such a comparison.

Method. The drugs were administered orally to 17 volunteers, 10 of whom were normal medical students, and 7, patients convalescent from minor ailments on the wards of Bellevue Hospital. The ages ranged from 23 to 50. There were 15 males and 2 females. All observations were carried out in a room or ward in which the illumination was constant. The subjects were kept at bed rest for a period of at least 20 minutes during which time observations were made of the pulse rate, pupillary size and reaction, oral secretions and mental status (dizziness, lightheadedness, tinnitus and teichopsia). Following this control period, the drug was administered and similar observations were made every few minutes for a period of 1½ to 3 hours and then at greater intervals for the remainder of the day. A definite change in any of the symptoms or observed signs was considered as evidence of toxicity. In 15 cases, increasing doses of the drugs were given on successive days in the attempt to reach the point of minor toxicity. Such a procedure would incidentally be of value in the detection of a cumulative action of novatrine.

Results, and Discussion The results are summarized in Table 1. The problem under investigation was to determine the minimal toxic dose of novatrine as compared to that of atropine, without reference to the use of this drug in any particular clinical condition. Therefore, essentially normal persons were employed as subjects. In the normal human being, however it is extremely difficult to distinguish between full physiologic effects and minor toxic symptoms of atropine and its congeners. Consequently, though it was appreciated fully that some of the criteria for minor toxicity might really represent full physiologic effects, the first definite changes in heart rate, pupillary size, oral secretions and mental status were considered evidences of minor toxicity.

* Formerly known as novatropine. For complete description see New and Non-Official Remedies American Medical Association, Chicago, p. 315, 1946.

TABLE 1.—COMPARATIVE TOXICITY OF ATROPINE SULPHATE AND NOVATRINE

Case No.	Age	Sex	Wt. (kg.)	Diagnosis	Atropine sulphate: Dose (mg.)	Tachycardia	Mydriasis	Oral secretions	Mental	Novatrine: Dose (mg.)	Tachycardia	Mydriasis	Oral secretions	Mental	Ratio
1	25	M	66	N	2.60	+	+	+	0	27.0	0	0	0	0	1–>10
2	25	M	55	N	2.60	+	+	+	+	32.5	0	0	0	0	1–>12½
3	25	M	75	N	2.60	+	+	+	+	27.0	0	0	0	0	1–>10
4	26	M	77	N	2.15	+	+	+	+	32.5	0	0	0	0	1–>15
5	25	M	66	N	2.13	+	+	+	+	27.0	0	0	0	0	1–>13
6	22	M	64	N	2.15	+	+	+	+	54.0	0	0	0	0	1–>25
7	26	M	75	N	2.15	+	+	+	+	68.0	0	0	0	0	1–>32
8	23	M	66	N	2.15	+	+	+	+	68.0	0	0	0	0	1–>26
9	25	F	57	N	2.60	+	+	+	+	88.0	0	+	0	0	1–>40½
10	25	M	70	N	2.15	+	+	+	+	68.0	0	+	0	0	1–>32
11	45	F	73	Enteritis	1.30	0	±	+	0	50.0	0	+	0	0	1–>38
12	50	M	66	Mucous colitis	3.25	0	±	+	0	273.0	+	+	+	±	1–>84
13	23	M	51	Renal calculus	2.15	0	±	+	±	90.0	0	0	+	±	1–45
14	45	M	59	Chole-cystitis	3.25	0	0	+	+	220.0	0	0	+	+	1–67.7
15	38	M	73	Fr. tibia	2.60	+	0	+	0	150.0	0	0	0	0	
16	40	M	59	Fr. tibia	2.60	0	+	+	0	180.0	+	+	+	0	1–>62½
17	40	M	66	Fr. tibia	2.15	+	+	+	0	120.0	0	+	+	0	1–50
												+	+	0	1–60

N, normal medical student; 0, no change; +, ++, +++, maximum change (*i. e.*, increase in heart rate of 30 to 40 beats per minute; full pupillary dilatation and extreme dryness of the mouth). All mental changes consisted of slight dizziness.

In the first few experiments small doses of novatrine were given but it soon became evident that they had neither toxic nor cumulative effects and subsequently very large doses were exhibited. This cautious attitude explains, in part at least, the failure to obtain a true toxic point in the early subjects.

Seven individuals were made toxic (in the sense already defined) with novatrine, in doses ranging from 68 to 273 mg. and averaging 143 mg. The minimal toxic dose of atropine for these same persons ranged from 2.15 to 3.25 mg., with an average of 2.54 mg. The corresponding ratio of minimal toxic doses of atropine and novatrine ranged between 1:32 and 1:84, with an average ratio of toxicity of 1:54. In this connection, it is noteworthy that not only were fewer subjects intoxicated with novatrine but that, with 2 exceptions, these reactions were quantitatively less severe than the reactions experienced after atropine.

Conclusions. 1. The average ratio of minimal toxic dose of atropine and novatrine was 1:54.

2. No cumulative effect was observed after daily administration of large doses of novatrine.

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CONCENTRATED AQUEOUS HEPARIN

A New Form of Intramuscular Administration

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The importance of intravascular thrombosis and its attendant morbidity and mortality now is generally realized. Interference with the coagulation of blood by the administration of an appropriate drug is a feasible and logical approach to the problem of intravascular thrombosis. Of the substances employed for this purpose heparin most nearly approaches the ideal. Its intravenous administration, even in interrupted form, is attended by too many difficulties to permit of general use. Loewe and his collaborators[1] have reported the use by the subcutaneous route of heparin in Pitkin's menstruum. Dicumarol is also commonly employed, having the advantage of oral administration. The necessity for frequent prothrombin determinations during its administration, the occasional occurrence of serious bleeding from overaction of the drug and the inability to arrest this excessive action promptly limit its use. Neither heparin in its present forms of administration nor dicumarol meets the requirement of an anticoagulant which can be administered simply, safely, painlessly and accurately for the general prophylaxis and therapy of venous thrombosis.

This communication describes the clinical utilization of a new preparation of concentrated aqueous heparin which can be administered intramuscularly. It has proved valuable in inhibiting coagulation in thrombophlebitis, phlebothrombosis, postoperatively as prophylactic therapy against venous thrombosis and as an adjuvant to the use of dicumarol in various thrombotic states. The total number of cases (115) treated has been small and inadequate for statistical analysis but the technique of the use of the drug has been so simple and the justification for its widespread use so apparent that our experiences should be recorded at this time.

Studies with the intramuscular administration of heparin in the dilute solution (10 mg. per cc.) commercially available, led us to the use of a concentration of 100 mg. in 1 cc. Such a solution of concentrated aqueous heparin,* free from foreign substances or the vasoconstrictor agents and watery in appearance and viscosity, has been administered intramuscularly under our supervision for about a year. The medication was usually injected by nurses into the gluteal muscles with the regular intramuscular syringes and needles at 8 to 12 hour intervals. Individual doses of heparin have varied from 50 to 180 mg., the smallest doses being given to patients weighing 90 pounds or less and the largest to those over 180 pounds. Our data are not complete enough at the present time to permit the formulation of exact schedules of administration, for patients vary in their heparin requirement. We have not attempted to ascertain the reasons for this except to observe a rough correlation with the body weight. Adequate prolongation of the coagulation time of the blood is usually attained in patients weighing between 100 or 130 pounds by administering 100 mg. every 8 hours or 120 to 140 mg. every 12 hours. In heavier individuals larger doses may be required. The maximum

* Prepared and supplied by the Lederle Laboratories, Pearl River, New York, through the kindness of Dr. Stanton M. Hardy.

daily dose should not exceed 450 mg. The successful heparinization in patients weighing over 170 pounds may be obtained by giving 1 mg. of heparin per pound of body weight as the initial dose and between 0.5 and 0.7 mg. of heparin per pound at 8 hour intervals subsequently.

The medication was administered over a period of several months to most of the postoperative patients of a general surgical service, including a considerable number of thoracic cases and sympathectomies for hypertension. The cases were not selected; the ages varied from 17 to 70 years (though the majority of the patients were over 40 years) and both sexes were included. Many of the patients were febrile because of their disease and received other medication such as vitamins, blood transfusions, sulfonamides or penicillin. Since a considerable number of cases of carcinoma are included, the nutritional and metabolic status of not a few of the patients was poor. Almost all were in bed. The administration of heparin was usually started 24 to 72 hours after operation and was continued for a variable period or until the patients were out of bed and walking. There was no existing intravascular thrombosis in this group of 90 patients and none developed venous thrombosis. Bleeding at the site of operation was observed several days after the inception of the heparin regimen in 3 cases early in the series. It was found that this complication could be averted if the anticoagulant were withheld until 48 to 60 hours had elapsed after operation. In a second group of 25 patients, most of whom had recently experienced thrombophlebitis or coronary artery thrombosis, bleeding was not observed. Hemorrhage into an internal organ was never observed.

TABLE 1.—THE EFFECT OF A SINGLE INTRAMUSCULAR INJECTION OF CONCENTRATED AQUEOUS HEPARIN ON THE COAGULATION TIME OF 18 DIFFERENT PATIENTS

Weight of patient (lbs.)	Heparin (intramus.) (mg.)	Coagulation time* (peak)	Coagulation time† (last test)	Time of last test‡
110	100	3	−2	1½
118	150	8	6	2½
121	175	0	−5	1½
210	200	35	0	20
150	200	88	−2	20
150	200	80	6	20
110	160	40	40	5½
120	175	78	78	5½
149	150	20	10	12
108	150	35	35	8
129	150	28	28	8
118	150	65	35	8
150	150	35	20	12
151	150	12	12	8
156	150	12	12	8
180	180	29	20	8
122	120	15	10	8
168	170	10	10	8

* The number of minutes above the control coagulation time at the peak of the effect of heparin.

† The number of minutes above (or below) the control coagulation time when the last test was performed.

‡ The number of hours after the injection of heparin that the last test (previous column) was performed.

One of the practical advantages of this method of heparin administration was the ease with which the anticoagulant effects could be controlled. In our first trials the coagulation times (Lee and White method) were performed at frequent intervals in order to insure an adequate but not extreme anticoagulant effect. At the present time 1 coagulation determination daily, immediately before the administration of a dose, is found to be adequate. If the result of this test reveals complete cessation of heparin effect, a dose some-

what larger than the previous one is given. If, on the other hand, a satisfactory prolongation of the coagulation time (18 to 24 minutes) is observed, the dosage is not changed. If the coagulation time is found to be over 24 minutes, either a smaller dose is ordered or the injection is postponed for 2 hours. Coagulation tests done at other intervals after injections reveal prolongation beginning ½ to 1 hour after the initial injection. The greatest prolongation is observed 4 to 6 hours after needles. In only rare instances did a hematoma appear at the site of injection and this was never large. A reaction which occurred in 2% of the injections consisted of a palpable and occasionally tender nodule up to 3 cm. in greatest dimension. Frequently the patients were not aware of these nodules which were absorbed despite continuation of the drug. In a small number of instances included in the above, nodules were not palpable but patients complained of some pain at the site of

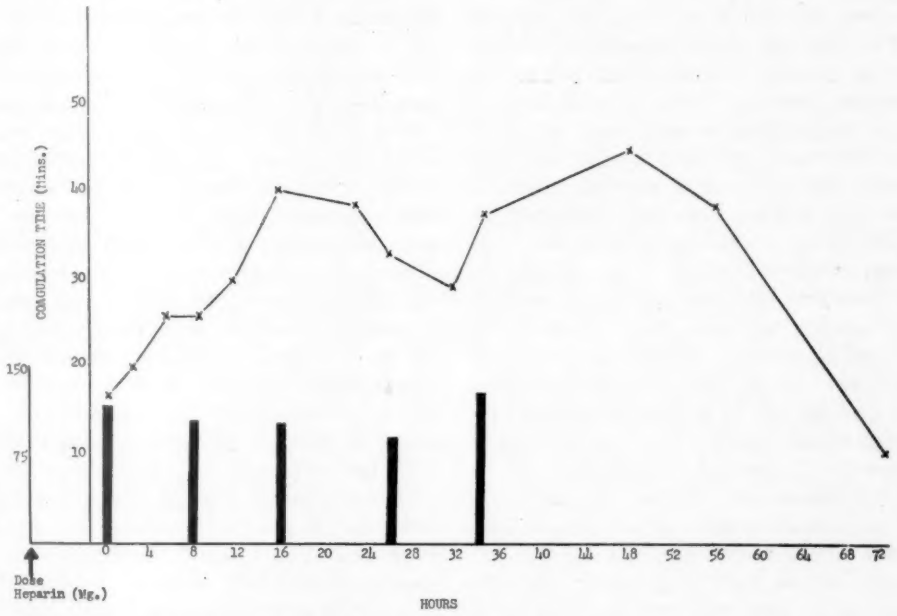

CHART 1.—The effect of repeated intramuscular injections of concentrated aqueous heparin on the coagulation time.

an injection, and, with the doses of heparin which we administer, varies between 25 and 60 minutes. Prothrombin or other determinations are not required. The table and chart which follow illustrate some of the effects mentioned.

As previously noted, the injections were given with the usual syringes and needles, specifically 20 gauge, 1½ inch needles. This technique was followed in order to maintain the customary ward routine. Since the heparin is in an aqueous medium, it can be given easily with 22 or 24 gauge injection. This was never severe enough to require analgesics. With the use of finer needles, the incidence of local reactions probably could be reduced.

In the small series of cases of thrombophlebitis that we have treated, we have observed the same rapid subsidence of fever, tenderness and edema in the affected extremity that others have described with different preparations of heparin or other anticoagulants. Some of these patients were treated for periods as long as 3 weeks.

We have taken advantage of the prompt

action of heparin in administering it to 10 patients who were concurrently treated with dicumarol. Approximately 48 hours after the commencement of the conjoint therapy, the heparin was discontinued when the prothrombinopenic effect of dicumarol was evident.

Summary. Concentrated aqueous heparin (100 mg. per cc.) is a new, simple, safe and essentially painless form in which the drug can be administered intramuscularly in order to achieve a desired anticoagulant effect.

The authors wish to express their gratitude to Dr. Myron Steinberg for assistance with part of this work.

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DEGENERATIVE BONE DISEASE

Findings in 18 Cases With Posterior Spurs of the Lumbar Vertebræ

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The presence of spurs or osteophytes on the posterior aspects of the bodies of the lumbar vertebræ has not received much consideration. Therefore it seems desirable to describe 18 cases. In reviewing the literature relatively few references are listed. Two recent articles in the foreign literature[13,14] describe sciatica produced by thickening of the posterior margins of the lumbar vertebræ or by posterior spondylarthrosis. Bailey and Casamajor[1] in 1911 report 1 case of spinal "osteoarthritis" in which a posterior spur was considered to be the cause for compression of the spinal roots in the lumbar area, and Parker and Adson[8] in 1925 reported 5 patients in whom bony spurs of the lumbar spine were thought to be the cause of low back pain and definite neurologic changes. In the latter report the Roentgen examination revealed only lateral exostoses but at operation "an overgrowth of soft, spongy, vascular bone producing a marked narrowing of the spinal canal was found." Larmon[6] in a study of 10 unselected spines obtained at autopsy found that "posterior lipping of the fifth lumbar vertebræ occurred in 4 specimens. In each case the osteophyte formation was located in the foramina and produced narrowing of the anterior diameter. All cases were associated with moderate to severe degenerative changes in the disk substance. Compression of the nerve root was evident in 2 of the spines." Although most writers do not mention the presence of such spurs, Shore[9] makes a definite statement after the examination of 106 spines from an anatomic museum and osteophytes never occur on the posterior portion of the bodies of the vertebræ.

In the cervical region the presence of spurs projecting posteriorly has received considerable attention during the past few years. The spurs may involve several cervical vertebræ or may be limited to only one. These osteophytes may encroach upon the nerve canal causing various symptoms and lead to serious neurologic changes which may partly be due to the anatomical arrangement of the cervical spine in which the roots emerge from the dura mater at right angles and also the factor that the intervertebral foramina decrease in size from the upper to the lower cervical vertebræ whereas the corresponding spinal nerves actually increase in size.[3] Hadley[4] has shown from cadaver specimens how the foramina in the cervical region may be reduced to one-fourth normal size by bony or fibrous tissue encroachment and nerves "crowded into the lower portion of the opening or become flattened in a ribbon-like manner or even completely destroyed." Several investigators[5,7] believe the condition follows damage to the intervertebral disk at the site of the bony spur rather than pressure of the spur itself on the root. Spurling and Scoville[10] state that "in many instances the herniated portion of the disk is surrounded by bone and that these bony prominences may project into the intervertebral foramina."

The incidence of posterior spurs in the lumbar area as observed in the writer's experience is shown by the following figures. In the 7 months covered by this report, 7251 patients were admitted to an Army general hospital in New Guinea. During this time the Roentgen ray department examined 910 spines; of these, 629 involved the lumbo-sacral region. Eighteen cases (approximately 3%) of the lumbo-sacral examinations showed spurs arising from the posterior surfaces of the

bodies of the vertebræ. To compare the incidence of this lesion with that of the usual arthritic conditions of the spine: a diagnosis of osteoarthritis was made in 168 cases with the familiar hypertrophic changes of lipping on the anterior or lateral aspects of the vertebræ. Fifteen cases of ankylosing spondylitis or rheumatoid arthritis of the spine were found. During a preceding 22 months period the same hospital organization functioned in Australia. During this time the total hospital admissions numbered 33,000 and a total of 2800 examinations of the spine were made. However, only 1 case of a posterior spur was reported while in Australia. The incidence of osteoarthritis and rheumatoid arthritis of the spine was relatively the same during the 2 periods.

Analysis of the 18 cases in this series reveals that the average age was 33 years ranging between 21 and 39 years. Two-thirds of the patients recalled an acute injury to their backs which required bed rest or cessation from their civilian work for a varying period. The time between the initial injury and the admission to the Army hospital varied from 3 months to 25 years with the average approximately 6 years. Many of these patients did have symptoms after entering the Army; however, only 2 were unable to complete the strenuous basic training of a soldier. All the men were sent overseas, and it was not until they suffered a second injury or their discomfort became severe did they finally enter the hospital.

The symptoms in the lower back on admission varied from mild discomfort to severe disabling pain. In 2 patients the complaints were typical of osteoarthritis, that is, they were of a dull aching nature aggravated with changes of position and of the weather, whereas in the other 16 patients the symptoms were similar to the herniated disk syndrome with pain worse at night and on coughing or sneezing, with a history of partial or complete remissions between attacks and with radiation of pain down the posterior part of the leg to the foot or down the lateral or medial aspects of the thigh. The examination of 12 patients showed the loss of diminution of the normal lumbar curve, spasm and tenderness of the lumbar muscles, limitation of motion in the lumbar area and a positive straight leg raising sign. The Achilles tendon reflex was absent in 3 patients and paresthesia of the leg was found in 1 patient.

The laboratory findings included: a complete blood count which was normal in all cases; the blood test for syphilis was also negative in all cases; the sedimentation rate was elevated in only 1 patient in whom a diagnosis of rheumatoid arthritis of the spine was also made. Lumbar punctures were done on all the patients. The spinal fluid determinations of globulin, gold curve and Kahn were normal in all patients. The total protein of the spinal fluid of the 18 cases ranged between 16 to 48 mg. with the average for the group of 30 mg.

The Roentgen rays in the straight lateral view demonstrated the presence of these spurs on the inferior aspects of the bodies of the vertebræ. They were found on the second lumbar vertebra in 1 case, on the third lumbar vertebra in 3 cases, on the fourth lumbar vertebra in 4 cases and on the fifth lumbar vertebra in 10 cases. The size of the spurs measured from 2 to 6 mm. in length. A spinogram with oxygen was done on 1 patient. The air column showed a slight impression upon the anterior subarachnoid air column which was the sight of the bony spur. A filling defect at a lower level was also found. This patient had minimal objective signs.

None of these patients was subjected to operation while overseas. Several were returned to the United States for further observation and treatment while others were returned to duty, and thus no further information is available.

The clinical history and findings of 2 illustrative cases are as follows:

Case Reports. CASE 1. Patient P. R. was a 21 year old white male who in civilian life

injured his back while diving 2 years before admission to the hospital. He had difficulty during his basic training and was placed on light duty. The pain in his back was constant, worse at night and aggravated by changes in the weather. There was no radiation of the pain. The examination disclosed a loss of the lumbar curve, tenderness on pressure of the lumbar vertebræ, the lumbar muscles were tender and spastic, the motion of the back was limited in all directions due to pain and the straight leg raising sign was positive on the right. No other abnormal neurologic findings were found. The laboratory work was normal. The Roentgen ray (Fig. 1) showed a large bony spur with

FIG. 1.—Posterior spur on inferior aspect of body of fourth lumbar vertebra.

almost complete bridging on the posterior inferior aspects of the body of the fourth lumbar vertebra.

CASE 2. A 37 year old soldier, 3 years before admission, suffered an injury to his back which kept him in bed for 3 weeks. He had no difficulty in his strenuous army life until 1 month before entering the hospital, when on attempting to crawl out of a trench, he was taken with acute pain in his back so that he had to be carried to the hospital. The pain was constant and was aggravated by coughing and standing. He was transferred to the general hospital after the acute symptoms had subsided at which time the physical examination revealed only tenderness on palpation of the lumbar vertebræ. The motion of the back was normal and no neurologic changes were found. The Roentgen ray (Fig. 2) showed a posterior spur on the body of L-3 with considerable lipping on the anterior margins of all the lumbar vertebræ.

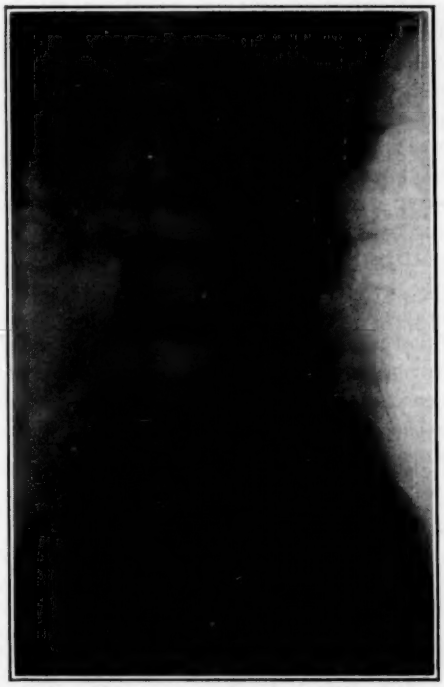

FIG. 2.—Posterior spur on posterior aspect of the body of third lumbar vertebra and spurs on anterior aspects of other vertebræ.

Discussion. Why do the spurs develop in these particular areas? Many investigators believe that degenerative changes in the spine are the result of lesions in the intervertebral disks. The idea is proposed that either complete or partial rupture of the nucleus pulposus may occur with subsequent degeneration and evidence of proliferation of the margins of the bodies of the vertebræ. Keyes and Compere[5] in their study of the intervertebral disk show that with damage to the disk, the weight

of the body is transferred to the lateral and anterior portion of the vertebra leading to sclerosis and lipping of the spine. They injured the disk posteriorly in dogs and allowed the nucleus pulposus to exude and found in a period of 3 months at the site of the injury "a marked hyperostosis and new bone formation very similar to that observed clinically in cases of marked osteoarthritis of the spine." In the cervical area Stockey[11] noted the secondary calcification of the nucleus pulposus due to herniation. Stress and strain or improper mechanics have been considered by Bennett and Bauer[2] who found that by displacement of the patella in rabbits they were able to produce marked lipping of the femur in a period of 4 weeks. The occurrence of exostoses at the margin of the vertebræ in scoliosis also lends support to this idea. Changes in blood supply have been suggested as a possible etiologic factor and there are those who favor an infectious process, a form of local infection in the joint or area. Weems[12] considers an inflammatory process as the cause of calcification of disks in children since in childhood these structures have a blood supply so that infections elsewhere can be carried to them by the blood stream.

The interpretation of the symptoms and clinical findings depend upon the position of the spurs and any change they may undergo. These osteophytes may have been present before the latest attack, and it was not until some pathologic change, as yet unknown, in the local area made their presence manifest.

This study is presented to call attention to the presence of these spurs in the lumbar area which are apparently more frequent than is usually considered. This report may encourage further observations and lead to additional speculation as to etiology.

Summary. 1. A survey of 629 spine examinations made in patients with low back pain showed posterior spurs of the bodies of the lumbar vertebræ in 18 cases.

2. Signs of root irritation were found in 12 cases.

3. Due to the exigencies of military service, these patients could not be followed sufficiently to prove the relationship of spurs to symptoms.

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THE RÔLE OF PULMONARY VESSELS IN THE REFLEX CONTROL OF THE BLOOD CIRCULATION*

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Research done during the last decades has substantially enlarged our knowledge of the reflex control of the blood circulation. This research has particularly demonstrated the great importance of the neuroreflex influences which arise in the cardiovascular system itself. To the number of such thoroughly investigated reflexes which regulate blood circulation and are connected with the activity of the pressoreceptors of the vascular bed of the systemic circulation, belong: the depressor (cardio-aortic) reflex, the carotid sinuses reflexes, and the superior and inferior vena cava reflexes.

Thanks to these data, the hypothesis about reflex "self-regulation of the blood circulation" has, at present, a firm foundation through an immense factual material. However, all these scientific data are not perfect because we are still lacking the knowledge of the inner mechanics and interrelations of the known reflexes, and also because we are still without a full knowledge of all reflexes regulating the blood circulation. Particularly the pressoreceptor rôle of the vessels of the lesser blood circulation has been quite insufficiently investigated. For this reason we decided to devote our research to this problem.

Experimental research previous to ours on the pressoreceptor function of pulmonary vessels was conducted by 3 workers only: Schwiegk[14] (1935), Schweitzer[13] (1936), and de Burgh Daly and co-workers[2] in 1937. Of these studies, only the work of Schwiegk gave more or less clear indications that the reflex influence of increased blood pressure in pulmonary vessels changes the rhythm of the heart rate and the condition of the blood-vessels of the systemic circulation.

However, the literature on this subject has many data which indicate indirectly the possibility of reflexes from pulmonary vessels. In this class belong first of all the experimental and clinical observations on the pulmonary embolism which show that not only are the mechanical factors important but also equally so the neuroreflex factors which play a great rôle especially at the initial stage of the embolism.

Although almost all authors agree that the priority in this question belongs to the German scientists, Schumacher and John[12] (1914), our extensive study of the literature on the subject convinces us that the honor of this discovery belongs without any doubt to 2 Russian scientists, A. Fokht and B. Lindeman.[5] In 1908 these men demonstrated that after the section of the pulmonary branches of the vagus nerve an embolism produces less disturbance of the cardiovascular activity. They emphasized the function of reflex factors in the whole symptom-complex of an embolism of a pulmonary artery.

A series of clinical observations of the pulmonary embolism forced many others, such as Sauerbruch,[10] Edens,[4] Frey,[6] Binger and Moore,[1] to come to the same conclusions.

The experiments of Scherf and Schönbrunner[11] in 1937 raised the question of a possibility of reflexes from pulmonary vessels on the basis of a similarity between electrocardiograms of an embolism of a pulmonary artery and of a myocardial infarct due to a thrombosis of the ramus descendens of the left coronary artery. As, at the autopsies of 2 patients who had

* A lecture given at a special meeting of the Philadelphia Physiological Society and the Philadelphia Chapter of the American-Soviet Medical Society.

the above-mentioned symptoms during their illness, these authors did not find any organic changes in the myocardium or coronary vessels, they concluded that the essence of the lesion lies in a spasm of coronary vessels produced by the reflex action from the pulmonary vessels.

However, subsequent observations of many authors did not support the existence of such a "pulmo-coronary" reflex.

Morphologic data also lead us to believe that reflexes from pulmonary vessels may exist. Thus, long ago, in 1898, a Russian histologist, Dogel,[3] described numerous nerve endings of sensory type in the walls of the pulmonary artery. Analogous findings have been reported by many authors up to the present day.

Taking into consideration the absence in the literature of exact information upon the reflexogenic rôle of pulmonary vessels, we decided to pursue these facts further.

As to the choice of experimental methods, we followed principally the basic methods of Schwiegk.

Methods. For the experiments we used cats weighing 2 to 3 kg. Under chloroform and other anesthesia, we cannulated the right common artery and vena saphena magna. At the same time we performed tracheotomy and intubated the trachea. After that, through a cannula in the vena saphena, we injected a 10% solution of urethane. Following this, the entire experiment was conducted under urethane anesthesia. Having induced an artificial respiration, we opened wide the left half of the chest and cannulated the left pulmonary artery and ligated the pulmonary veins of the same side. As a result, the left lung kept its innervation intact, but was completely isolated from the main blood circulation. The gas exchange evidently was performed only by the right lung. The cannula in the left pulmonary artery was connected with rubber tubes filled with Bayliss 8% gum acacia Ringer solution and also connected with a mercury manometer and with a simple device which allowed changing of the pressure in pulmonary vessels.

In all experiments a mercury or membrane manometer was used for registration of the pressure in the right common carotid artery. In some series of experiments, electrocardiographic registration was taken, also venous pressure and pressure in one of the branches of the pulmonary artery of the right lung, which was not separated from the main blood circulation; also in some series of experiments changes of the volume of the spleen were taken, etc. Briefly, we made 103 experiments of this kind.

Results. In all our experiments in which the operation was accomplished without complications and the animal was in good condition, increase in pressure in pulmonary vessels which had been separated from the general blood circulation always induced a fall of blood pressure in the arteries of the greater circulation, and also in most instances, the pulse rate was diminished. This fall of pressure in the arteries of the greater circulation was clearly indicated even at comparatively small increases of pressure in the pulmonary vessels (see Figs. 1 and 2).

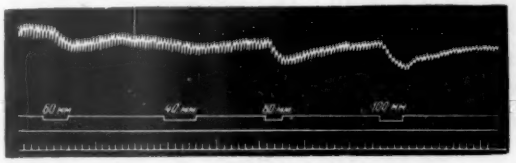
The fall of arterial pressure of the greater circulation showed a definite ratio with the increase of pressure in the pulmonary vessels. Figures 1 and 2 indicate the character of this ratio. The fall of the pressure starts after a latent period of about 2 to 3 seconds. With repeatedly increased pressures in pulmonary vessels, the reaction showed a tendency to a gradual diminution, which could be attributed to the development of a pulmonary edema.

The reflex character of the phenomenon is fully confirmed by the results of experiments in which the section of the left vagus nerve on the neck was accomplished. Thus, Figure 3*A* showed a common reaction. Figure 3*B* demonstrates a curve which has been registered during the same experiment, but after the section of the left vagus nerve. There is no change of pressure in the right common carotid artery, despite the increase of pressure in pulmonary vessels up to the very high level of 100 and even 130 mm. of mercury.

If we analyze the reactions due to increase of pressure in the pulmonary vessels, we come to the conclusion that these reactions, as a rule, are results of the change

in frequency of heart beat (heart component) and also the change in vasomotor reaction of vessels of the greater circulation (vasomotor component). In some experiments these components manifest themselves quite independently. However, in the majority of cases, the reaction is a result of simultaneous changes from the heart and from the blood-vessels.

The changes in pulse rate are usually



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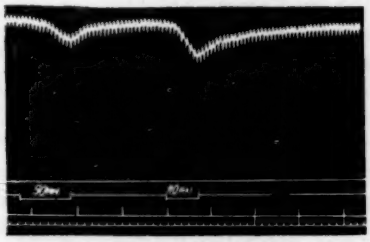

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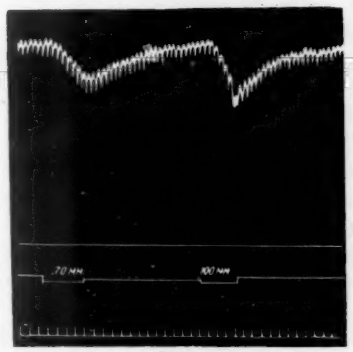
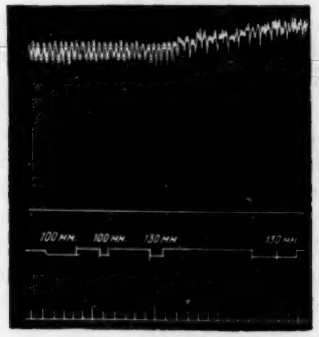


3 A



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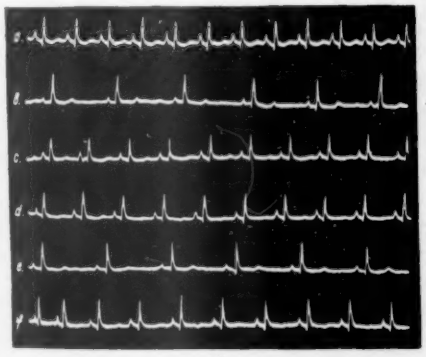

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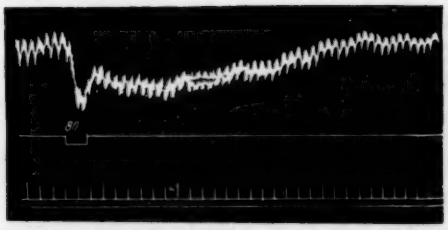

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FIG. 1.—Fluctuation in the carotid pressure produced by distention of the left lung at pressures as indicated. Cat. Time record at 10 second intervals. (4/9/39.)

FIG. 2.—Experiment of the same type as Figure 1. (5/7/39.)

FIG. 3*A*.—Responses as before with intact vagus. (5/9/39.)

FIG. 3*B*.—Repetition of the experiment after section of the vagus.

FIG. 4.—Effects of lung distention on the pulse rate as indicated by the electrocardiograph. (*a*) Control; (*b*) 80 mm. pressure in pulmonary vessels; (*c*) 40 seconds and (*d*) 80 seconds after release of pressure; (*e*) repeated distention of pulmonary vessels; (*f*) return to normal. (12/2/39.)

FIG. 5.—Reaction to distention showing a marked after-effect. (12/1/39.)

very pronounced and consist on the average of a diminution of the rhythm from 25 to 30% in comparison with the starting level. In a few cases, we see a diminution of the rhythm of more than half. For a more detailed analysis of the reaction of the heart we performed many experiments with electrocardiographic registration of the heart activity. These experiments convinced us that the changes of the heart activity are expressed only in the slowing down of the rhythm without any great changes of the form of the curve, or conduction time, etc. A typical example of these experiments is given in Figure 4. The results of these experiments are quite contrary to the above-mentioned results of Scherf and Schönbrunner, who claim the existence of the pulmocoronary reflex.

We believe that our findings show without any doubt that the electrocardiographic changes of myocardial infarct type in cases of the embolism of the pulmonary artery are due only to mechanical disturbances of blood circulation and gas exchange, and express only different degrees of oxygen lack of the myocardium, and do not present any reflex influences.

Coming to the analysis of the vasomotor component, we will first describe the reaction of the arterial part of the vascular tree. The absolute depth of the fall of the arterial pressure showed individual variations. Taking the average, in the majority of cases, the increase in the pressure of the pulmonary vessels of 40 to 50 mm. of mercury induced the fall of the pressure in the arteries of the greater circulation of 20 to 30 mm. At a higher starting level of arterial pressure, its fall as the result of a reflex from pulmonary vessels was more sharply marked. The fall in pressure occurred, as a rule, without variations, reaching the peak 25 to 40 seconds after beginning of the stimulation. In a few instances, however, the fall in pressure occurred so rapidly, that the curve showed a great similarity to the classic curve which results from stimulation of the peripheral end of the vagus nerve.

In the majority of cases, the curve of blood pressure showed considerable after-effects, reaching up to 20 to 40 seconds and in some cases even more. An example of this is Figure 5. As to the mechanism of the vasomotor response, we believe that in our case the fall of the arterial pressure is the result of the pronounced dilatation of the arterioles in different parts of the systemic circulation entirely similar to that produced by depressor or carotid sinus reflexes. In support of this fall of the vasomotor tonus we too found a considerable increase in the amplitude of the pulse pressure at the time of the reflex response.

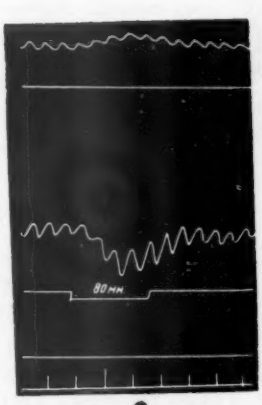
To elucidate the changes occurring in veins, we made a series of experiments and registered the venous pressure (jugular vein, by means of a water manometer). The results were absolutely similar: in all cases we registered an increase in venous pressure. This is illustrated in Figures 6 and 7. The character of these changes is quite evident and does not need comment.

We did not obtain identical results in our experiments when trying to register the blood pressure in a branch of an artery of the other lung, which was not excluded from the blood circulation.

We observed in the opposite pulmonary artery pressure changes which were not large and at the same time not consistent in the direction of the response. Still, we must remember that the question of participation of pulmonary vessels in depressor and carotid reflexes is still not absolutely settled and is undergoing further investigation.

Inasmuch as the spleen is regarded as a "blood depot" and plays an active rôle in many vasomotor reactions of the organism, we decided to study this organ in connection with these reflexes, especially as the spleen is so easily accessible for experiment.

In these experiments with oncographic registration of the volume of the spleen, we found that this volume increases in



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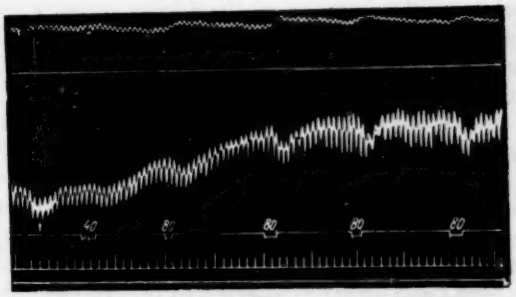

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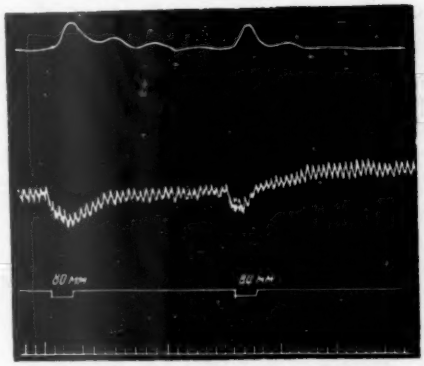

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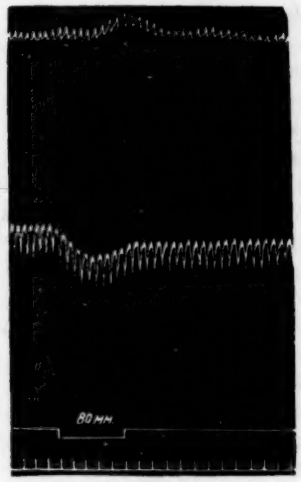

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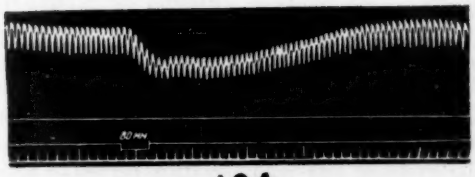

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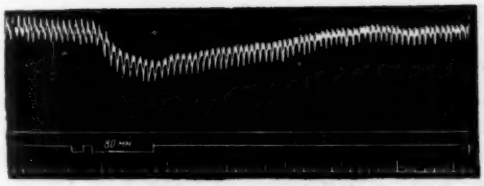

10B

FIG. 6.—*1*, Record (top) of pressure in the right jugular; *2*, base line of jugular pressure; *3*, arterial pressure; *4*, signal; *5*, base line of arterial pressure; *6*, time 10 second intervals. (11/3/39.)

FIG. 7.—Observations as in Figure 6. (11/17/39.)

FIG. 8.—Record of splenic contraction and blood pressure as a result of the distention of the left lung. Time in 10 second intervals. The splenic record is shown above and the arterial pressure below (6/7/39.)

FIG. 9.—Record of the same type as Figure 8. (6/9/39.)

FIGS. 10*A* and 10*B*.—Record 10*A* was obtained with a distention of the pulmonary vessel and 10*B* was obtained later after the denervation of carotid sinuses in the same animal. (11/22/39.)

proportion to the increase in the blood pressure in the pulmonary vessels. This reaction (increase of volume) evidently shows the active participation of the spleen in the general fall of the systemic arterial blood pressure, reflexly elicited at the increase of pressure in pulmonary vessels (see Figs. 8 and 9). The active part the spleen plays in these experiments could be demonstrated when the spleen nerves were cut. In such cases we saw complete lack of any reaction of the spleen when the spleen was denervated.

We also tried to investigate the interrelation of this reflex with those from the carotid sinuses. In the study of the functional interrelations between separate pressoreceptor zones of the greater circulation, 2 kinds of facts are recognized.

It was found that, by simultaneous stimulation of both depressor or both sinus nerves, the fall of pressure is greater than by the stimulation of only one of them. There exists, therefore, a definite physiologic summation.

These interrelations present, in our opinion, a real physiologic interconnection between the 4 pressoreceptor nerves of the arterial part of the greater circulation, because in natural conditions the pressure changes during a given period of time simultaneously in the whole beginning part of the arterial stream.

The receptors which are situated in the aorta and the carotid sinuses are, thus, simultaneously subjected to equal stimulations by intravascular pressure and send equal impulses to the centers which control the blood circulation.

We think that it is quite different with the second series of facts on the basis of which conclusions about a definite antagonism between pressoreceptor nerves are made. In the conditions of an experiment, such an antagonism, a definite counteraction of the intact pressoreceptor zones to the change of the pressure caused by the stimulation of the central end of one cut pressoreceptor nerve, is sufficiently established. Hering,[7] for instance, found that in case of preservation of the normal innervation of one carotid sinus, the stimulation of the central end of the other sinus nerve gives a smaller effect than after cutting of the sinus nerves on both sides. Hering found the same also in respect to the depressor nerves. The same interrelations are found between carotid sinuses and depressor nerves in similar conditions of experiments.

The essence of this antagonism consists in that (due to the tonic character of the stimulation of the pressoreceptors which occurs reflexly under the influence of the isolated artificial stimulation of one of them), the fall of blood pressure lowers the intensity of inhibitory impulses from other pressoreceptors which preserved the normal connection with the vascular stream.

As a result, we find an opposite picture, the pressoreceptors become no longer brakes, "a bridle," as picturesquely described by Hering, but stimulators, "a whip," the pressure shows a tendency to an increase, thus counteracting a complete expression of the effect of an artificial stimulation.

We believe that this antagonism has no real physiologic importance and exists only in the specific artificial conditions of an experiment which radically distorts the normal interrelations between conditions prevailing in separate receptor zones. We have already emphasized that in actually physiologic conditions the pressure in the region of all pressoreceptors of the arterial part of the greater circulation can, in a certain period of time, change only in the same way, so that the receptors of the aorta and of the carotid sinuses are in regard to the intravascular pressure always under similar conditions.

In our experiments, the increase of this pressure occurred in a vascular region which was excluded from the general blood circulation. The conditions of our experiments could, therefore, to a certain degree be compared with an isolated stimulation of one separated sinus or depressor nerve while the other receptor zones were intact, or can be compared with an increase of pressure inside of a sinus isolated from the

blood circulation (*e. g.*, according to the "*cul de sac*" method of Moissejeff.[9])

In order to elucidate this question, we made a series of experiments with an increase of pressure in pulmonary vessels before and after a denervation of the carotid sinuses.

In all experiments, we recorded the reaction of the blood pressure on an increase of the pressure in the pulmonary vessels at first with normal innervation of the carotid sinuses. Then we denervated both sinuses, and after a while we repeated the experiment after the denervation.

As a result of our experiments, we saw in the majority of cases relations similar to those which, as previously described, are seen in analogous conditions between carotid and depressor reflexes.

An example of such an increase of the effect after denervation of carotid sinuses is seen in Figure 10B. In this experiment, the increase of the pressure in pulmonary vessels to 80 mm. Hg caused a fall of pressure in the carotid artery to 40 mm.

At the same time, a considerable prolongation of the period of the after-effect is to be seen; 4 minutes after the first stimulation and 3½ minutes after the second, the pressure had not returned as yet to the starting level (before denervation of the carotid sinuses, the period of after-effect in this particular experiment is also quite considerable; however, 2 minutes and 40 seconds later, the pressure had already reached the previous level).

In some experiments we did not notice any remarkable increase of the reaction after denervation of carotid sinuses, in the sense of a greater depth of the fall of pressure. We observed, however, almost always a marked prolongation of the period of after-effect.

If we take into consideration that during our experiments we almost always observed a tendency to a gradual weakening of the strength of the reaction and to a shortening of the period of after-action in the course of an experiment, then the changes just mentioned obviously clearly express the change of the reaction after denervation of the carotid sinuses.

To sum up, we think that we are entitled to the conclusion, based on the series of experiments, that in case of a functional exclusion of the carotid sinuses, the reflex from the pulmonary vessels is characterized by a greater intensity.

We believe that we can prove that an increase of pressure in the vessels of a lung which has been excluded from the general blood circulation, causes extensive changes of the whole circulatory system which have incontestably a reflex character.

These changes consist in a reaction of the heart (slowing down of the rhythm) as well in vascular changes (extensive dilatation of the vessels). The basic character of the hemodynamic change in the investigated reflex is accordingly analogous to the reactions observed in depressor and carotid reflexes, though it is not so strong as the latter. Therefore, the reflex from pulmonary vessels should, together with the depressor and carotid reflexes, have an appropriate place among the reflex mechanisms which play an important rôle in the "automatic" regulation of the blood circulation.

From the general point of view, the investigated reflex should be classed as to type and number with the so-called moderator-reflexes ("*Entlastungsreflexe*" of Hess[8]) of the cardiovascular system. In the greater circulation, similar reflexes originate as a result of a stimulation by the increased pressure of the pressoreceptors which are situated in the beginning part of the arterial stream (aorta, carotid sinuses).

The physiologic meaning of these reflexes consists in securing of changes which return an increased pressure to a more or less normal level which would not cause an overload of the heart.

From this point of view, the depressor reaction at an increased pressure in the vessels of the lesser circulation is fully analogous to the reaction which can be

observed at increased pressure just in the arterial part of the greater circulation.

On the basis of such considerations, one can theoretically assume that the present reflex originates in the arterial stream of the small circulation.

De Burgh Daly assumed that the reflex, which interests us, originates in the sensory endings in pulmonary veins, but we think it strange to assume, from the point of view of the physiologic significance of proprioceptive reflexes of the cardiovascular system, the presence of a reflex of a depressor type at an increase of pressure in the venous part of the vascular stream. Actually, the increase of the venous pressure manifests itself usually as a result of a functional deficiency of the heart and a further weakening of the heart activity in these conditions (depressor reaction) would be unable to restore the blood circulation toa norma level, It would on the contrary increase the degree of deficiency and result in causing a peculiar vicious circle.

In analogy to reflex regulation in the greater circulation, it is known that the increase of pressure in the vena cava causes not a depressor reaction but a pressor one, increase in frequency of the heart action and a slight increase of arterial pressure (Bainbridge reflex, 1920). As a result of the increase of the heart action, the filling of the venous part of the vascular stream is diminished and thus this reflex plays a substantial rôle in the regulation of the whole blood circulation. In our opinion, the same should be expected in regard to the pulmonary veins and we regard the venous part of the pulmonary vascular tree also as a possible source of origin of reflexes not of depressor but of a pressor nature.

We think it necessary to clear this question by a new series of experiments with a perfusion of pulmonary vessels, *i. e.*, in conditions near to the normal in the meaning of interrelation of pressure between arterial and venous parts of the pulmonary vascular stream.

In regard to the functional significance of the reflex from pulmonary arteries, we have already mentioned that the character of the obtained reactions shows that it undoubtedly represents a typical moderator reflex. The specific situation of receptor zones of this reflex in the arterial part of the pulmonary circulation reflects its predominant rôle in preventing an overload of the right heart.

In such increases of pressure in the arterial part of the pulmonary vascular stream as they may arise in a number of physiologic and pathologic conditions (Valsalva's experiment, embolism of the pulmonary artery, and others), the reflex from pulmonary arteries, by lowering of the heart action and by causing a transfer of the blood into the greater circulation *via* an extensive vasodilatation and an increase of the capacity of the depôt, prevents the weak musculature of the right ventricle from being overburdened by work. At the same time, this reflex has probably some significance in the prevention of a pulmonary edema which, as is well known, easily occurs in a case of a prolonged increase of pressure in the system of the pulmonary artery.

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OBSERVATIONS ON THE VELOCITY OF THE BLOOD IN NORMAL MEN IN THE BASAL STATE*†‡

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Measurement of the velocity of the blood by determining elapsed time between injection of material intravenously at one site and evidence of its appearance at another is in wide popular use as a diagnostic measure. In a recent study of convalescence[5] we tested blood velocity with the material described by Spier, Wright and Saylor[6] commercially available as Macasol.¶ Kvale and Allen[1–4] have worked with this same material, reporting normal standards much like those found by Spier, Wright and Saylor. Discrepancies between our findings and those above mentioned led us to reëxamine the standards for this test and assess its variability in our own hands. We find a normal range of blood velocity significantly greater than previous workers and a significant difference in the average blood velocity as well. Our findings indicate that measurement of the blood velocity is not as useful as many believe because the relatively wide range of "normal" values overlap the "abnormal" values in the very cases where the differential significance of the test would be most important.

Material and Methods. Of 46 normal men, each was in the basal state, that is, had not eaten since the evening meal the night before and either remained in bed until the test was done or returned to bed for an hour after reaching the laboratory. Of these men, 34 were military personnel who had completed the reconditioning program at Thayer General Hospital which included a 10 mile hike under full pack; 12 were civilians who had been hospitalized some months before but who had returned to usual health, were engaged in their ordinary activities and showed no clinical evidence of disease. The mean age of the men tested was 25.6 years; the extremes were 18 to 40 years.

Instructions were given to the subject in a stereotyped way with reassurance that nothing untoward would happen. The subjects were supine. The arm with the largest antecubital vein was drawn a little away from the body and supported at about the level of the auricle. The vein was entered cleanly with an 18 gauge needle and the tourniquet released several minutes before the test. Two ml. of Macasol were injected as rapidly as possible. The stop watch was started at the beginning of the injection. The observer reported times to a recording assistant as the patient announced end points at the tongue, the hands, the perineum and the feet. After subsidence of all sensation from the first test, a second test was carried out through the same needle. No attempt was made to distinguish between time to the right and left hand or to the right and left foot.

The mean of the 2 tests was entered as the circulation time for that individual. In the statistical analysis standard deviations were based upon these means and the number of individuals tested. This differs from the

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† Thayer General Hospital patients were studied through the coöperation of Brigadier General Henry C. Pillsbury, Officer Commanding, Lt. Col. Richard Stetson, Chief of the Medical Service, Major Donald Ferguson, Chief of the Reconditioning Service and other members of the staff.

‡ This work was done in the Lung Station of the Department of Medicine, a laboratory organized under a grant from the Commonwealth Fund, and some of the equipment used was available through a grant by the Ciba Pharmaceutical Products, Inc.

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¶ Supplied through the courtesy of the Nepera Chemical Company, Yonkers, New York.

analysis employed by previous authors[1,6] in that they derived standard deviations from the total number of tests done rather than the number of individuals tested.

Close scrutiny of our data revealed a systematic difference between 2 observers. In 16 cases tested by Observer A the mean arm to tongue circulation time was 18.1 seconds whereas an entirely comparable group (tested actually on the same days and in the same place) showed a mean of 13.4 seconds and the difference was statistically significant. Part of this difference was found due to the habit of 1 observer to read the watch to the mark ahead of the moving hand while the other read to the mark behind in tests conducted with a pendulum appearing from behind a partition. While this difference could amount only to a second, recalculation of the data corrected for this no longer showed a significant difference between observers.

On 1 occasion evidence of anxiety influencing the test was apparent. In a ward of Thayer General Hospital 15 soldiers were distributed 7 along one wall and 8 along the opposite. Explanation of the test had been given the night before and all were under supervision through the night. Tests were made early in the morning before the men had risen. Preparations were made in an adjoining room. Two teams entered quietly and moved

TABLE 1.—CIRCULATION TIME IN SECONDS TESTED WITH MACASOL

"Normal subjects" of both sexes reported by other authors compared with "normal men" in the basal state reported in this paper.

Subjects	Circulation time in seconds, arm to: Tongue	Perineum	Hands	Feet
Spier, Wright and Saylor:[2]				
35 normal subjects, 40 tests:				
"Resting"—mean	14.6	21.5	26.2*	27.9*
average deviation	± 3.23	± 4.59	± 5.26	± 7.1
range	7–22	12–32	11–43	10–48
Kvale and Allen:[3]				
13 normal subjects, 73 tests:				
"Basal"—mean	13.8	21.2	23.6*	34.1*
standard deviation	± 2.65	± 5.14	± 5.74	± 9.65
range—class	5–24	10–34	10–39	15–59
51 normal subjects, 102 tests:				
"Resting"—mean	13.7	21.0	23.5*	32.1*
standard deviation	± 3.52	± 5.52	± 6.04	± 9.59
range—class	5–29	10–44	10–44	20–69
Men reported in this paper:				
46 normal men, 92 tests:				
"Basal"—mean	16.7	26.0	28.1	37.4
standard deviation	± 4.8	± 8.4	± 6.6	± 9.5
range	9–30	13.5–56	18.5–48	23–63

* Average of right and left hand or right and left foot.

TABLE 2.—EFFECT OF ANXIETY ON BLOOD VELOCITY

Successive reconditioned soldiers tested in an open ward. Coefficient of correlation between time of injection and observed arm to tongue time is 0.66 ± 0.28.

Elapsed time from entry on ward (min.)	Arm to tongue time (seconds): Observer A	Observer B
8	14	10
16	17	9
24	15	13
32	Blank	14
40	22	14
48	21	11
56	20	18
64	30	No test
Mean	19.8	12.7

RESULTS. Our data are presented in Table 1 together with the results of Spier, Wright and Saylor[6] and of Kvale and Allen.[1] The arm to tongue time was 16.7 ± 4.8 seconds, the arm to perineum time was 26 ± 8.4 seconds, the arm to hand time was 28.1 ± 6.6 seconds and the arm to foot time was 37.4 ± 9.5 seconds.

down the ward. Tension was obvious in the men first tested, while the later subjects relaxed as they saw no ill befall their predecessors. As the teams moved down the ward, there was a progressive increase in the circulation time observed. We estimated the time of each injection from the start of the experiment. These elapsed times are tabulated with the corresponding arm to tongue time in Table 2. It is apparent at once that there is a correlation between the time elapsing from the start of the test and the observed blood velocity. The coefficient of correlation is highly significant statistically.

Correlations were attempted between circulation time and the height, weight, age and pulse rate of those subjects where these data were available and none was found. The variation in all of these measures was small, however, due to the nature of the subject material. No seasonal difference was observed between 2 groups studied, 1 in mid-summer, the other in early winter.

Discussion. The results reported by Spier, Wright and Saylor[5] give only "average deviation" while Kvale and Allen[1] based their "standard deviation" upon the total number of tests rather than upon the number of individuals, so, exact statistical comparison is impossible. It is evident that our mean times are longer in all categories than are those of the other observers. In the case of the arm to tongue time our mean of 16.7 seconds is 2.1 and 2.9 seconds longer respectively than that of Spier, Wright and Saylor and that of Kvale and Allen.

We followed the analysis we used because it has been shown[1] that variation of blood velocity is greater from individual to individual than upon repeated testing in the same individual. Since practical interest centers in comparing an individual to a "normal standard" it appears wise to broaden the biological base in the statistical analysis. Thus, if one enters the calculation of the standard deviation with the best estimate of circulation time available for the individual, which is the average of duplicate or multiple determinations, one minimizes the consistency of results in the same individual and emphasizes the variation between individuals. For this reason, pooling of all values irrespective of the individuals from whom they arise seems to us an erroneous approach because it takes no true account of the number of individuals tested; that is, the real size of the biological sample.

Our data on convalescent patients reported elsewhere[5] illustrate the error into which one might have been led by accepting the narrow "range of normal" previously reported. Convincing evidence that our convalescent patients were indeed within the normal range was obtained when follow-up studies upon return of these patients to normal health revealed a mean change of only −0.4 second in arm to tongue circulation time; *i.e.*, no change at all.

It seems unusual that there was no difference between blood velocity in basal subjects and blood velocity in subjects who had merely rested for a few minutes as found by Kvale and Allen.[1] We have no data on this point but there were only 13 subjects in their "basal" group and perhaps a larger sample might have revealed a higher mean. Another point concerns sex differences where again we have no data. The observations of others have not been broken down to show sex difference.

When the standard deviation is calculated in a manner to give due weight to biological variation it is seen that a considerable latitude must be allowed for "normal" circulation time. The extremes of our observed range were 9 to 30 seconds for arm to tongue time. The ±1 standard deviation is considered to include approximately 68% of cases and ±2 standard deviation which is commonly considered a more reliable "range" includes 95% of cases. From our data these ranges would be from 11.9 to 21.5 seconds, or 7.1 to 26.3 seconds respectively. If the clinician chooses the smaller range he must resign himself to error 1 time in 3.

No untoward reactions of any kind occurred. Two of our 46 subjects experienced no end-point reaction. One patient, not a member of this normal series, seemed to "pool" the material in his arm because, while no end-point sensation occurred at first, later, as he moved his arm to arise, he experienced the spreading sensation characteristic of this agent. Kvale and Allen[1] have discussed fully other factors in "blanks," a term used to designate failure of the subject to perceive a sensation of warmth in the area.

The evidence of the effect of anxiety is interesting. One may question whether a patient exhibiting anxiety is "basal" and obviously he is not in the academic sense of the word. However, in practical use of any physiological test, experience has shown that anxiety is frequently encountered and contributes to the variability in results whether in normal subjects or patients who are ill.

Summary and Conclusions. 1. Duplicate determinations of the blood velocity of 46 normal male subjects in the basal state were made with the calcium-magnesium salt mixture of Spier, Wright and Saylor[6] (Macasol).

2. The arm to tongue time was 16.7 ± 4.8 seconds, the arm to perineum time was 26 ± 8.4 seconds, the arm to hand time was 28.1 ± 6.6 seconds and the arm to foot time was 37.4 ± 9.5 seconds.

3. These times are significantly longer than those reported by Spier, Wright and Saylor[6] and by Kvale and Allen.[1] This discrepancy is discussed.

4. The normal variation of blood velocity is greater than commonly recognized. This variation impairs the accuracy of this test as a diagnostic measure among the patients in whom otherwise it would be most useful.

5. Systematic differences occurred between the data of the 2 observers and a reason was found to account for this discrepancy.

6. In addition to many previously reported factors affecting the determination of blood velocity, anxiety as a factor could be evaluated in one of our experiments.

7. There was no simple relation between the velocity of the blood and the height, weight, age or pulse rate of these normal young men nor was any seasonal variation perceptible.

8. No untoward reactions of any kind occurred and end-points were secured in all but 2 subjects.

9. One additional reason for "blanks" is described.

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FURTHER CONSIDERATION OF THE QT INTERVAL

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Part I. Introduction. So much has been written about the measurement of systole, both mechanical and electrical, that any further comment must reasonably be accompanied by new information. Three types of information will be presented: (1) a description of the "bundle of His" as it appears in the human fetal heart; (2) measurements of QT duration in various species; (3) data acquired in acute experiments designed to modify the QT interval. In addition, deductions regarding cardiac diagnosis as well as the deductions concerning intraventricular conduction will be made.

The terms "mechanical systole," "electrical systole" and "Q–T" as they appear in the literature should be defined. Any 1 of the 3 terms indicates a measurement of ventricular contraction. When measurements are made by the use of mechanical devices such as suspension levers, cardiac plethysmographs, delicate levers (or mirrors) attached to the heart, pressure manometers of various types, or by the recording of heart sounds, the term "mechanical systole" is employed. The measurements obtained are conditioned not only by the physiologic state of the heart being investigated but by the specific characteristics and mechanical limitations of each different recording device. When the electrocardiograph came into general use the term "electrical systole" appeared. This period was measured from the beginning of the Q wave to the end of the T wave and was supposed to include the time required for 4 processes, namely: the passage of the action current over the bundle of His, and over the ventricular muscle; the actual ventricular contraction; and the recovery. Electrocardiographic explanations have changed with the years; Burch and Windsor[6] now write:

"The Q–T interval represents the time required for depolarization and repolarization of the ventricular musculature. This interval coincides *closely* with ventricular systole, as systole begins, essentially, with the peak of the R wave and ends with the termination of the T wave. The interval is measured from the beginning of the QRS complex to the end of the T wave (see Chapter I). It varies considerably with age, sex, and cardiac rate. When the rate is rapid the interval is short and when it is slow the interval is long."

"The Q–T interval *varies inversely with the calcium level of the blood.* In hypoparathyroidism, uremia, after vomiting or forced breathing, if the calcium blood level is low, the interval is prolonged. In hyperparathyroidism if the blood calcium level is high, the interval is shortened. Digitalis shortens the interval. Toxic states, myocardial ischemia, and many types of cardiac disease, such as rheumatic, diphtheritic, arteriosclerotic, and hypertensive, prolong the interval. A prolonged Q–T interval frequently indicates the presence of myocardial intoxication. This may or may not be reversible."

Scattered quotations from the paper by Blair, Wedd and Young[5] add further viewpoints:

"In the intact heart, Q–T duration covers that time from the depolarization of the first activated area to the time of repolarization of the last area to recover. The well-known dependence of Q–T on heart rate is due not only to the cumulative effects of rate, but to each diastolic interval as it occurs. It is suggested that after exercise

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the Q–T interval may be a more sensitive index of the *state of the muscle* than is heart rate. It cannot be denied that there is a third factor determined by the heart rate which simultaneously arrests contraction and starts repolarization. It is very probable that the relation of the Q–T interval to the duration of the beat will ordinarily hold for the whole heart."

A starting point for analysis is offered by one further sentence contained in the summary of the article by Blair, Wedd and Young,[5] namely: "Evidence is presented that repolarization arrests the contractile process in the muscle leading to the conclusion that the electrical processes control the mechanical rather than the mechanical the electrical."

This phrase deserves emphasis. Ashman and Hull also regard the electrical change as primary: "Under normal conditions, therefore, the electrical change apparently induces the mechanical, that is, the local flow of action current in each segment of muscle initiates the contractile response in the same segment" (p. 16).[2] Thus, if mechanical and electrical recording were equally perfect one would expect contraction time and QT to be identical in a single cell. Also considering the entire heart, contraction in no part can begin before Q nor can contraction in any part outlast the end of T, provided the electrodes are optimally placed and sensitivity is adequate to record all that actually occurs. It is possible that recorded mechanical systole may be shorter than electrical systole (time required to develop tension, instrumental lag, etc.), but because contraction ends with repolarization mechanical systole cannot outlast electrical under the conditions specified. Hence any conclusions based on the measurements of mechanical systole which are longer than electrical systole must be rejected.[18] If mechanically recorded data agree with adequately recorded electrical data then conclusions based on measurements of "mechanical systole" may be used to corroborate those based on electrical measurements. However, if mechanical and electrical measurements do not agree, the latter must be accepted.

The clinician and the biophysicist seem in sharp disagreement when White and Mudd[29] write: "The measurement of the duration of the Q–T of the electrocardiogram is apparently of little or no clinical value," but Blair, Wedd and Young[5] state: "It is suggested that after exercise the Q–T interval may be a more sensitive index of the state of the muscle than is heart rate."

PART II. HISTOLOGIC STUDIES AND THEIR IMPLICATIONS. Critical reviews of the connections of the conducting system in various species can be found in the literature and need not be recapitulated here.[8,17,27,30] More recently it has been questioned whether the human heart (and that of the dog) really possess a conducting system composed of specialized tissue.[11] Nonidez[19] reports one present in dogs and monkeys and describes the parasympathetic nerve supply to this tissue.

Serial sections of 3 human fetal hearts were available in this laboratory for study; they were stained by Masson or Mallory techniques. One was supplied by the Carnegie Institute of Washington, courtesy of Dr. George Corner, and the others were prepared by Dr. Cornelius T. Kaylor of this University. In each of these human hearts, tissue which stains unlike ventricular heart muscle, and which has a connective tissue sheath can be identified.[21] When this tissue is reconstructed from the serial sections it is found to have a distribution similar to that commonly called the "bundle of His" and its branches and peripheral expansions as seen in ungulates. From the main bundle and from the chief branches of the bundle, multitudinous fibers emerge which can be followed, but only for short distances, until they imperceptibly change into cells having the same staining reaction and appearance as cardiac ventricular muscle (see Figs. 1, 2 and 3). All histologists have noted this imperceptible change which is invariably an axial (end to end) transition. These

FIG. 1.—A frontal section through the septum of the heart, showing above the membranous septum (collagen staining blue). The 3 upper arrows indicate the capsule (staining blue) of the bundle of His (staining mauve). The lower arrow indicates the left bundle branch streaming downward subendocardially. Note the numerous connections to septal muscle. (Mag. × 55.)

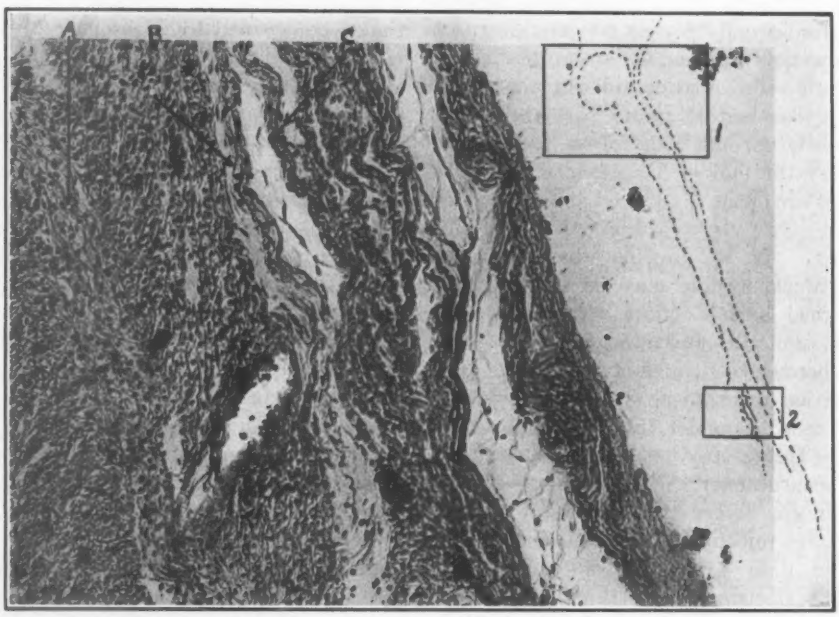

FIG. 2.—Detail of left ventricular margin of the septum. The photomicrograph shows 3 conducting system strands (see arrows *A*, *B*, *C*). Note that the tip of arrow *C* lies near the transition from the large clear-celled conducting fiber above to the narrower, less clear, more deeply stained muscle cell below. (Mag. × 215.) The pen sketch indicates the locale of Figures 1 and 2 on a different scale.

connections are numerous and strands continuously leave the main bundles, so that numerous small islands of muscle are supplied by successive offshoots.*

Discussion of Part II. Do what we have supposed to be physiologic facts agree with such an anatomic arrangement? several syncytia, why is it that so many physiologists have reported that there is no spread of current for any great distance along a single band on the surface of the heart?[12]

If small islands are successively activated, one must inquire: (*a*) Has syncytial

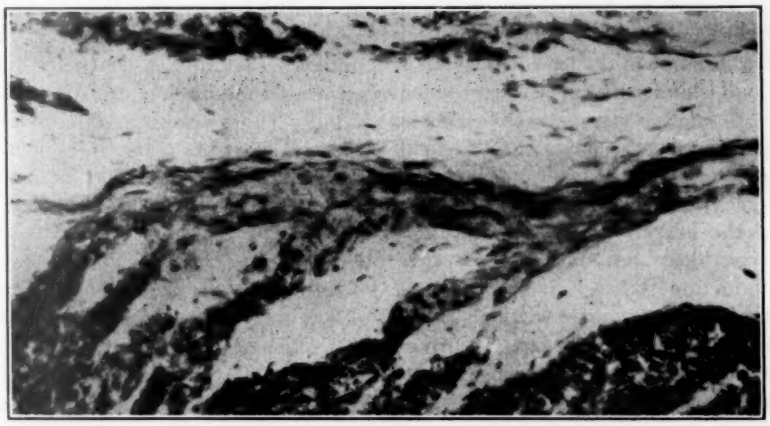

FIG. 3.—Heart of a 580 mm. long beef embryo. Terminal twigs of the conducting system enlarged 230:1. See S.54 a Purkinje fiber with 5 terminal transitions into heart muscle. (Wahlin. Figure 24.)

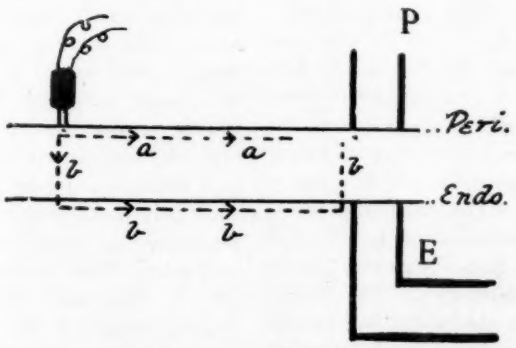

FIG. 4.—A diagram showing alternative paths (*a–a*, *b–b*) which an artificially induced excitation wave may take in the heart wall. (Lewis, Mechanism and Graphic Registration of the Heart Beat; courtesy of Hoeber, Inc.)

It has been said that the ventricular muscle is a syncytium, 1 huge interconnected mass of muscle. If this be so, first of all how could so many anatomists[22] be convinced that the mammalian ventricle is made up of several distinct muscle bands? Even if the concession were made, that the ventricles contain not merely 1 but spread over long surface areas been proven or disproven, (*b*) Is there evidence in the literature which would support this theory, and (*c*) What prevents generalized spread? Most writers have not found evidence of surface spread over long areas (consult Harris[12] for Bibliography). Reports of at last 3 investigators could be interpreted

* See also Truex, R. C., and Copenhaver, W. M., Am. J. Anat. **80**, 173, 1947.

to support the theory that limited areas of tissue are activated.

An experiment described by Lewis[14] (on page 92) is pertinent (see Fig. 4). Let us assume that when the path *b–b* was followed the stimulating electrodes were sufficiently separated from the epicardial contact to be on different "islands." Then, conduction had to be retrograde *via* a muscle cell and thence by a conducting path to a junction and then forward again to a second island. But note the sentence: "*If the stimulating electrodes are nearer to the contacts, the wave may reach P along the path a–a.*" Here is experimental proof that "syncytial" spread along the surface layer of the heart is very limited. This experiment does not necessarily prove that conduction is *faster* in the Purkinje tissue than in heart muscle, it does prove that from one point on the heart's surface an impulse can be driven in a retrograde manner and that eventually another surface area is activated. It does prove that an artificial stimulus did not spread across the surface syncytium when the stimulating and the recording electrodes were well separated (20 to 30 mm.). The conduction rate of heart muscle (on the surface) would need to be measured from 2 contacts sufficiently near to be on the same "unit." This experiment of Lewis suggests that such units are of macroscopic dimensions. The main difference between this experiment of Lewis and those of Robb and Robb[23] was the "nearness" of the 2 electrodes. The latter showed that if the electrodes were sufficiently near and a cut were made between them, the intrinsic wave failed to reach the distal electrode. Robb's hypothesis of conduction along a muscle bundle would need to be restated with this modification that there is not "syncytial" spread of depolarization along even 1 muscle bundle for any very great distance but that the "conducting" system is so arranged that successive areas along a given muscle bundle are depolarized sequentially. Moe, Harris and Wiggers[18] when analyzing the initiation of fibrillation write that their experiments failed to show that the fibrillating process necessarily spreads in the direction of surface bundles and specifically state: "Such observations disprove the possibility that development of fibrillation is contingent on passage of repeated long reëntrant waves over both ventricles by common fasciculi of fibers." However, Ashman and Hull[2] (page 48) write: "It is not unlikely that in the ventricles, as in the auricles, the impulses are conducted more rapidly lengthwise through muscle bundles than transversely. Yet the syncytial character of the muscle would seem to assure transverse as well as longitudinal conduction."

Because of the histologic arrangement described above, if a wave of depolarization sweeps from conducting tissue to heart muscle cells this movement has to be parallel to muscle fiber direction. Furthermore, in order to be recorded, the passage of current must be axial, because if a wave of depolarization started in the center of a cell (arriving on a non-existent pathway) and spread in opposite directions, these currents would neutralize and no potential would be recorded. Failure of stimuli to spread from one region to another is doubtless related to the refractory phase because if a wave of depolarization reaches adjacent areas *almost* simultaneously these areas would be resting and refractory at *almost* identical times also.

Quoting from Ashman and Hull (page 70):[2] "Alfredson and Sykes point out that in spite of the much larger heart with thicker walls in cattle, the QRS interval averages only 0.09 second against 0.08 for man. *This is further evidence that the intramural branches of the Purkinje net work are relatively poorly developed in man.*" This conclusion is not the only possibility; one is equally justified in concluding that the conduction system is so efficiently arranged in each species that the whole mass of the beef heart is activated about as quickly as is the whole mass of a human heart, and each of these is

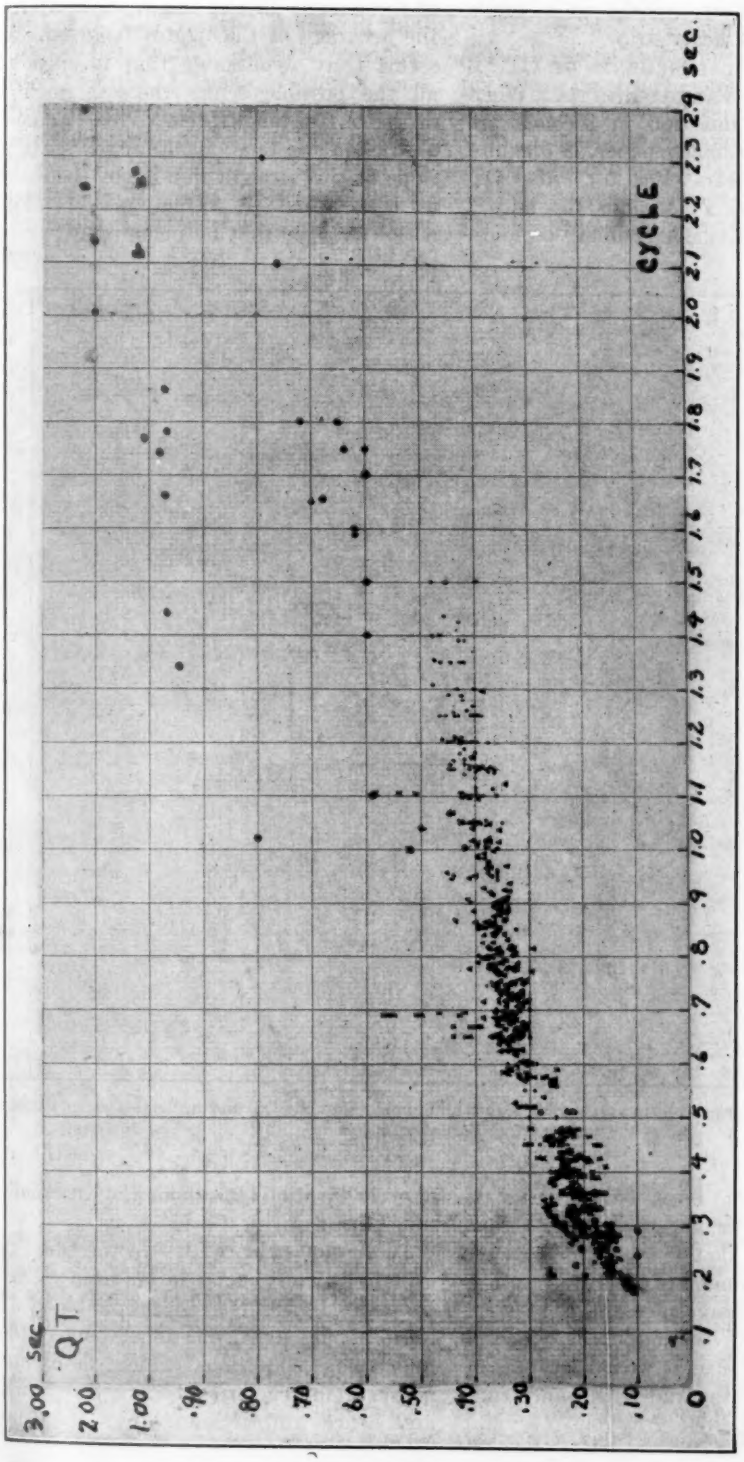

FIG. 5.—A scatter graph showing QT and cycle values:

activated about as quickly as a turtle heart, or a turtle heart strip.

PART III. MEASUREMENTS OF QT TO CYCLE RATIO IN VARIOUS SPECIES. When QT and cycle duration in seconds are plotted on coördinate paper, a definite relationship appears (Fig. 5). Also QT and cycle values in seconds for mice,[20] guinea pigs, rabbits, cats, babies,[7] puppies, medical students, dogs, calves, a goat, elephants,[28] turtles, and turtle heart strips[5] were plotted on double logarithmic paper (Fig. 6). The unanimity of the result is the more surprising since the data were obtained under divers conditions by many workers,[1,5,7,28,29] using various types of recording apparatus and with paper running at varied speeds. Any one or several of these many factors might have altered the accuracy of the figures reported. It seems truly remarkable that in spite of all the possible errors there is such a degree of constancy, for with little spread, a straight line relationship appears. The slope of this straight line is not the same as that found by Schlamowitz.[26] The reason may be that he included extremes of cycle duration far outside the "normal" range for man.

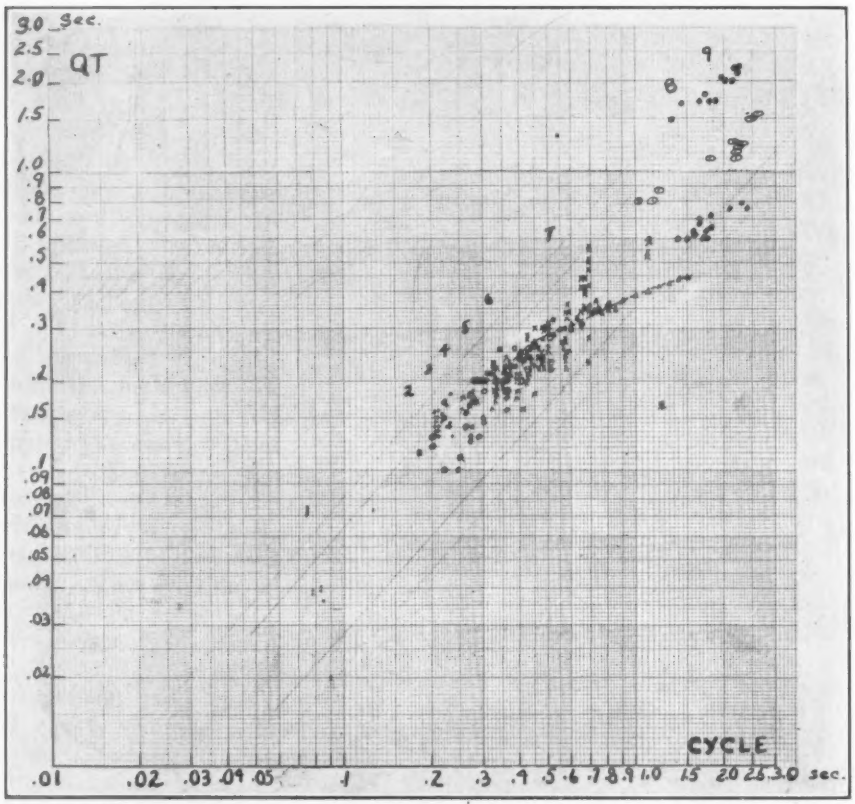

FIG. 6.—A scatter graph plotted on double logarithmic paper showing QT and cycle values for various species; symbols as in Figure 5

Discussion of Part III. In the effort to explain why any such relation from species to species, including even a "cold blooded" form, should exist, one must ponder the underlying conditions which determine heart rate, depolarization, repolarization and hence contraction. From mere in-

spection of the graph it is evident that mass of the heart is not the complete answer, for the QT values in turtle heart strips, intact turtles, elephants, dogs and medical students overlap at certain cycle values. If we consider, for example, Burnett and Taylor's[7] data for "reasonably healthy" young children, the younger the child the shorter is the QT. Also we know that the younger the child the higher is the metabolic rate. Among the various species studied, mice are at one extreme with the highest metabolic rates and turtles at the other with very low rates. A tabulation from Clark[9] and from Benedict[4] presents this information with species arranged according to weight.

The frog and the elephant are seen to have the same metabolic rates; a man, a pig and a mare have similar rates. Thus it is seen that when 1 species is compared with another, weight and metabolism do not bear a constant relationship.

If the same data are rearranged according to decrease in metabolic rate, the order is:

TABLE 1.—RELATIONS OF ANIMAL WEIGHT, HEART RATE AND METABOLISM RATE

Species	Weight (gm.)	Heart rate (min.)	Calories (kg. per 24 hrs.)
Mouse	1.75	700–1000	977
	12	670	639
	20	500	170
Frog	25	30	13
Tortoise	135	10–20	85
Guinea pig	400	267	94
Hen	1,000	354	110
Puppy	1,750	180	110–150
Baby	1,900	129	95
Hen	2,000	300–350	71
Rabbit	2,000	205	52
Cat	2,500	116–128	79.5
Baby	5,000	119	71
Dog	9,600	96	40
Baby	10,000	106	51
Goat	33,000	135	49.5
Man	66,000	55*	25
Calf	115,000	...	37
Pig	130,000	70–86	19
Percheron mare	450,000	55	22
Ox	500,000	24	43
Elephant	3,600,000	20–50	13

* This was the rate given in Clark's data, probably due to the special conditions of the study.

TABLE 2.—ANIMAL SPECIES ARRANGED ACCORDING TO DECREASING METABOLIC RATE

	Calories (kg. per 24 hrs.)		Calories (kg. per 24 hrs.)
1. Mice	170–977	6. Ox, 500 kg.	43
2. Hen, 1 kg.	110	Dog, 9.5 kg.	40
Puppies, 2 kg.	100–150	Calf, 115 kg.	37
3. Guinea pig, 400 gm.	94	7. Man, 66 kg.	25
Baby, 2 kg.	95	Mare, 450 kg.	22
4. Cat, 2.5 kg.	79.5	Pig, 130 kg.	19
Hen, 2 kg.	71	8. Elephant, 3600 kg.	13
Baby, 5 kg.	71	Frog, 25 gm.	13
5. Rabbit, 2 kg.	52	9. Tortoise, 135 gm.	8.5
Baby, 10 kg.	51		
Goat, 33 kg.	49.5		

The numbers in Table 2 which indicate groups having similar metabolic rates also indicate the species order on the QT/cycle graph (Fig. 6) with such overlapping as one might expect. The suggestion is made that the QT to cycle relationship depends on cardiac oxygen consumption which in turn is a considerable factor in the so-

called "basal metabolic rate." The deviation of points from the "normal" line in any species is at least partly a measure of the change in cardiac cellular activity. Such an intracellular change would not necessarily be correlated with cardiac murmurs, hypertrophy, or any specific disease. One would expect it to vary temporarily because of changes induced by chemical or hormonal agents acting transiently (or experimentally as the result of electrical stimulation) (Moe *et al.*,[18] page 490); and to be permanently altered when such agents acted continuously or when some more or less permanent change in the cellular protoplasm had occurred.

Several well-known formulæ[2,3,10,15] are available to express this relationship. But why so many formulæ, why a difference between men, women and children, why one constant for youth and another for age? Possibly because there are too many variables, possibly because the variables already studied (mass, age, blood calcium, etc.) are not the ones which really determine the duration of QT. In other words the formulæ are inadequate because each requires a "constant" but we do not know what action or effect the constant represents, nor do we know that it represents 1 only.

Ruskin and Decherd[25] have studied electrical systole of the rabbit heart and conclude: "The QT–RR curves are obviously not linear." They have failed to consider that the "isolated perfused rabbit ventricle" artificially driven may be activated in entirely different sequence than is normal and that this sequence may be different at different rates either due to shift of electrodes with activity or due to different cellular metabolic states at extremes of rates. Moreover, they include very slow and very fast rates which are certainly abnormal for a rabbit heart; *e. g.*, as low as 50 per minute and above 400 per minute. One should remember that for each species there is a spread of heart rates and a limited range within the spread which can be taken as characteristic for a particular species. Let us complete the quotation: "The QT–RR curves obviously are not linear, although in the central portion, excluding the slowest and fastest rates, the *deviation from linearity may not be great.*" Thus the data of Ruskin and Decherd[25] support Robb's opinion[24] that *within a range of rate normal for a given species* the QT–RR ratio is linear, although they came to a different conclusion. Schlamowitz[26] has already considered this matter and presented an analysis leading to the conclusion: "This curvilinear regression is not a better fit, statistically, than the linear regression."

If small areas of tissue are activated from one strand of "conducting" tissue, QT may be the time required for the depolarization and repolarization of such an island and QT would have the same duration whether 1 island or 1 million islands depolarized and repolarized, provided only all processes began and ended simultaneously. The fact that Blair, Wedd and Young's[5] turtle heart strips and White's elephant hearts[28] have QT intervals of similar duration could be interpreted in the sense that the "muscle strip" preparation is completely activated within a minimal time and that the multiple islands present in the elephant's heart are activated most efficiently. In larger hearts the "conducting" system is obviously longer and a longer time should be required for depolarization. *But* if depolarization of the conducting system does not register with ordinary electrocardiographic techniques (Ashman and Hull,[2] page 62; Bazett in MacLeod's *Physiology*,[16] page 284), if only surface effects register anyway, and if QT is a record of depolarization of ventricular muscle, then QT could not be expected to be longer merely because of longer conducting pathways, provided the individual islands of ventricular muscle to be depolarized in hearts of varying total size were of a similar area and as optimally connected, in large as in small hearts.

PR (or PQ) is the time elapsing from the first depolarization of auricular tissue (possibly the pacemaker but more prob-

ably auricular muscle) to the first depolarization of ventricular muscle itself (*not* the conducting system). Slowed conduction in the auricle, in the auriculo-ventricular connections, or a longer intraventricular pathway, would register as a delay in time between the onset of auricular and the onset of ventricular depolarization, that is, as a lengthened PR (or PQ) but not as a lengthened QRS or QT. This interpretation is substantiated by Ashman and Hull[2] (pages 69–70) and by Burch and Windsor[6] (page 63). PR varies with heart size.

Let us again quote from Ashman and Hull[2] (pages 69–70): "Those who have tried to interpret the human electrocardiogram in accordance with the newer view have been forced, in order to explain the normal width of the QRS complex, to assume that depolarization of a heart muscle fiber requires several hundredths of a second. If this be true, then conduction of the wave of excitation through ventricular muscle proper must be at an extremely low velocity, slower than in the turtle heart at much lower temperature." If we accept the view that QT is the time required for depolarization of a unit supplied by a single conducting strand, then in the intact heart a longer QT is due to some lack of simultaneity in the onset of depolarization and completion of repolarization of different units. We must not forget that if the wave of excitation did spread through any considerable extent of syncytium such a spread should have been detectable and this has not been the case either for normal hearts or for fibrillary waves.[12,18]

PART IV. EXPERIMENTAL MODIFICATION OF QT. *Method.* Some dogs were trained to lie in a cradle, on their backs, while epinephrine was given intravenously, either before or after administration of atropine. In other experiments dogs were given 30 mg./kg. of sodium pentobarbital after which the vagi were dissected and later were stimulated by electrodes leading from a Harvard Inductorium. Accelerator stimulation was performed before and after atropinization. Electrocardiograms were recorded by crystal galvanometers built by the Cambridge Instrument Company. The paper speed was generally 50 mm. per second.

Results. By direct experimentation in intact dogs one can show that to a limited degree absolutely and to a great degree relatively QT is shortened by vagal stimulation. In addition we observed that if the heart cycle is long due to certain non-vagal causes (*e. g.*, moderate asphyxia in an atropinized animal) QT is long, whereas if the same cycle duration is caused by vagal stimulation (or by acetyl beta methyl choline) the QT is unduly shortened. QT/cycle ratios during vagal stimulation in 4 experiments are shown in Figure 7 *B*.

During accelerator stimulation the actual QT reading may remain constant, or may increase slightly or even decrease but the ratio of QT to cycle increases greatly (see Fig. 7 *A*). Epinephrine injection in unanesthetized dogs causes first a reflex vagal stimulation and later a mixed vagal and accelerator stimulation (see Fig. 8). If epinephrine is given after atropinization in unanesthetized trained dogs the QT changes are the same as when the accelerators are stimulated (compare Fig. 7 *A* with Figs. 8 and 9 *G*). One sees that if the proportion of vagal and accelerator influence is varied the QT duration will change even though the cycle is unchanged. Figure 9 *A–B* indicates that in trained dogs the QT/cycle ratio averages about 40. During anesthesia this ratio is higher, averaging 53. During vagal stimulation there is tremendous reduction of this ratio even to 9 or 10. The average for the whole period of vagal stimulation is 23 (Fig. 9 *C*). If the vagus is reflexly stimulated by the administration of epinephrine, the same marked reduction of QT/cycle occurs (Fig. 9 *E*). The QT/cycle ratio is shown for accelerator stimulations in Figure 9 *D*. After atropinization the ratio is raised above 60, averaging 65 (Fig. 9 *F*). When epinephrine is given after atropine (Fig. 9 *G*), the

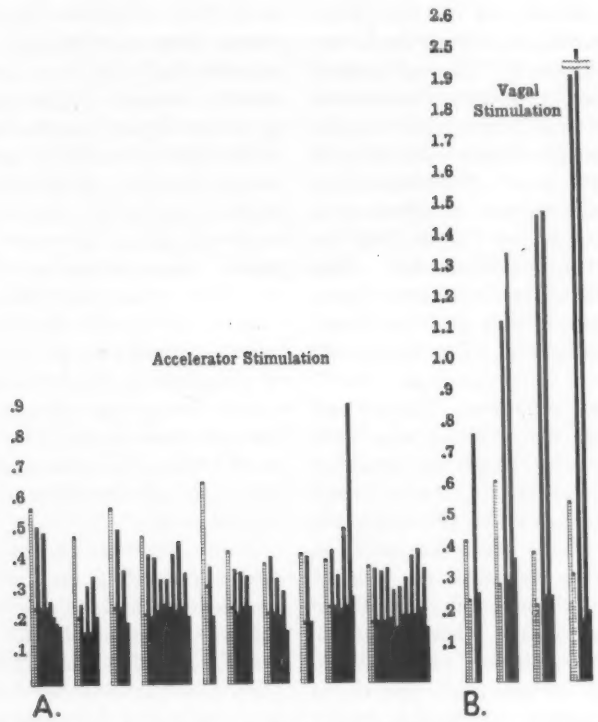

FIG. 7.—*A*, Accelerator stimulation in anesthetized dogs. Ordinates time in seconds. Taller columns represent cycle; following shorter columns are QT for same diastole. Cross-hatching control values, solid blocks result of stimulation. Data from 10 experiments. *B*, Vagal stimulation in anesthetized dogs. Results of 4 experiments. Times, cross-hatching and solid blocks have same significance as in 7 *A*.

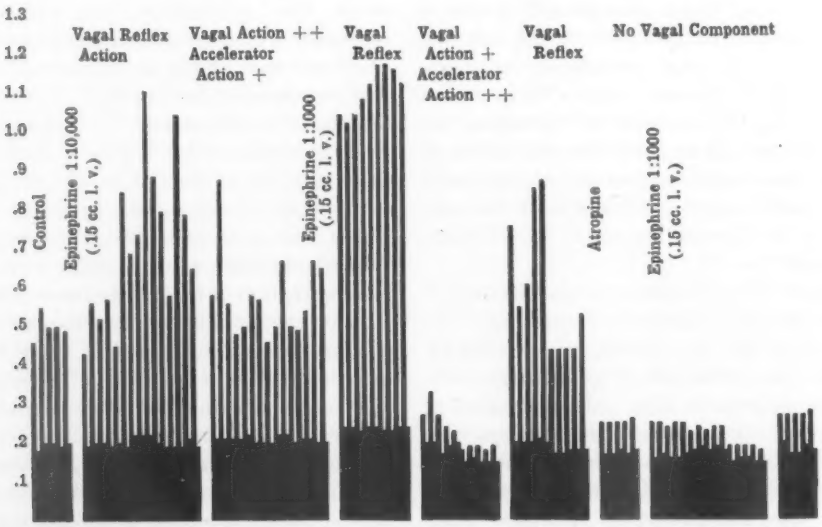

FIG. 8.—Data represent 1 experiment in a trained non-anesthetized dog, procedures indicated on graph. Comment in text. Ordinate represents time. Tall columns are cycle duration; following short columns are QT duration.

QT/cycle ratio becomes very high, even above 90.

Summary and Conclusions. 1. A "bundle of His" is present in the human fetal heart; this tissue merges imperceptibly (along a longitudinal axis) into heart muscle cells and a given strand supplies a limited area.

2. The possibility exists that this structure, "similar in distribution to the 'bundle of His' and its ramifications in ungulates," is not the "conducting" system. If it is not, if conduction from auricle to ventricle is by way of nerves, then since no parasympathetic nerves reach the ventricular muscle (Nonidez) the sympathetic nerves would need to be the "conducting tissue." As yet no method has been devised for differential sympathetic staining and the ultimate distribution of these nerves to ventricular muscle is not known. In other words, if the structure "similar in distribution to the 'bundle of His' in ungulates" does not serve as the conducting pathway from auricle to ventricle, then we know nothing about the anatomic distribution of a conducting system to the ventricle. Because cutting and crushing experiments damage *all* tissues in this region, such procedures can never determine which tissue serves as a conducting pathway.

3. In accordance with the distribution of this differentially stained tissue and in accordance with much data available in the literature regarding initial negativity of heart surfaces, it is suggested that quite limited areas of heart muscle, "islands," depolarize as a result of stimuli arriving over these numerous anatomic pathways.

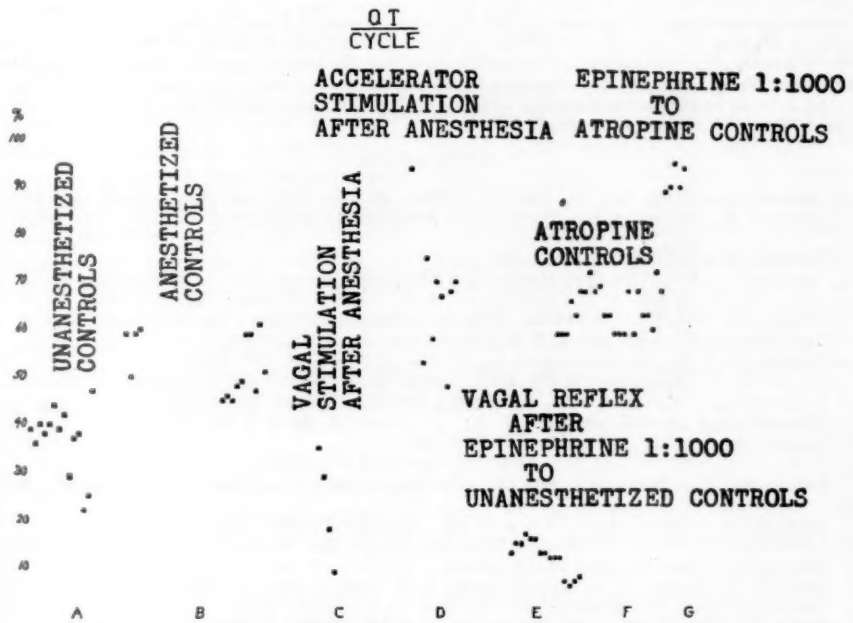

FIG. 9.—A scatter graph showing values of QT ÷ cycle, compiling the data in Figures 7 and 8.

4. QT readings for intact animals belonging to many species are presented and the relation of these to cycle length establishes that QT duration is independent of the total mass of the heart.

5. QT duration seems to be directly related to metabolism, presumably cardiac cellular metabolism.

6. In the intact dog, QT/cycle ratio is decreased by vagal stimulation.

7. In intact dogs, QT/cycle ratio is increased after atropinization and by accelerator stimulation.

8. Measurements of QT made under such conditions that the number of variables active at one time is limited offer an indication of the state of the heart muscle (*e. g.*, the effect of increased acetylcholine or epinephrine). Thus QT duration for a given cycle length can be varied at will.

9. The reason for lack of "clinical usefulness" of measurements of QT may be that the specific effects of all possible variables are not yet known.

10. In laboratory animals the QT/cycle ratio seems more significant than mere QT duration.

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EFFECT OF THYROID HORMONE IN TISSUE RESPIRATION

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Although much progress has been made in the treatment of hyperthyroidism, its etiology remains obscure. It is not known by what mechanism the thyroid hormone accelerates the metabolic rate. Moreover, the structure of the thyroid hormone, in its active form, has not been determined, although it is believed that thyroxin constitutes part of this molecule. However, since the active hormone is largely concerned with oxidative phenomena, it seems important to know more about alterations in biologic oxidations in the body cells of thyrotoxic subjects and about compounds that will modify these reactions.

The amount of oxygen consumed (QO_2) by many tissues of hyperthyroid animals has been stated to be increased, whether hyperthyroidism was produced by desiccated thyroid,[10,11] thyroxin,[7,8,13,14,17,18,22] or thyrotropin.[21,22] On the other hand, Gerard and McIntyre[10] found in thyroid-fed dogs that the QO_2 of thyroid tissue was decreased. After thyroidectomy the oxygen consumption of the tissues was shown to be decreased.[7,13] Reiss and associates[22] stated that the amount of thyroxin that theoretically could be mobilized from the thyroid gland by giving thyrotropin to rats would be ineffective in producing increased tissue respiration when given parenterally in the form of thyroxin. This observation could be interpreted as indicating that thyroxin must become activated before it has a calorigenic effect.

Haffner[12] believed that in hyperthyroidism there is an increased anaërobic glycolysis and that the increased oxygen consumption in this condition resulted from the necessity of the organism to oxidize or resynthesize the increased metabolites. However, results of the studies of these phenomena have varied.[9,18,20,22] In a thorough investigation of the subject, McEachern[18] concluded that an increase of tissue glycolysis is not the fundamental cause of the increased oxygen consumption in hyperthyroidism. He believed that there is no abnormal respiratory mechanism in the body cells. He found that hepatic and renal tissues from hyperthyroid animals oxidized various substrstes (lactate, pyrovate and succinate) as well as did normal tissues, while muscle oxidized them at a rate greater than normal.

In this laboratory we have investigated some of these problems; the results are reported in this paper. The main objectives of these studies were to observe: (*a*) the direct and indirect effects of thyroglobulin or thyroxin on the oxygen consumption of tissue slices; (*b*) the effect of common inhibitors of respiration on tissues of normal and hyperthyroid animals; and (*c*) factors affecting the activation of thyroxin.

Methods. The experiments were performed with rats, guinea pigs and patients with thyroid disease. The rats were of the white Wistar strain and varied in size and sex; most of them were males weighing about 200 gm. They were fed Purina Laboratory Chow. The guinea pigs were of both sexes and varied in size, although most of them weighed about 300 gm. They were fed rabbit chow, supplemented with lettuce and carrots. Basal metabolism tests were conducted with a closed-circuit method, a small spirometer being used for each rat. The air was circulated by a vacuum pump. Carbon dioxide was removed with flakes of sodium hydroxide and water was removed by concentrated sulfuric acid. The test was

conducted after the animals had fasted for 18 hours. The basal metabolic rate was determined in the manner described by Lee.[15]

For the studies dealing with the oxygen consumption of tissue slices the animals were fasted for about 15 hours and were killed by a blow on the head. The liver, kidney, diaphragm, pectoral muscle, heart and thyroid gland were rapidly sliced into pieces less than 0.5 mm. in thickness. All of the tissue for each experiment was obtained from the same animal, except that thyroid tissue was taken from 2 or more animals. Duplicate sets of determinations, including control specimens, were conducted and the values were averaged.

The rate of oxygen consumption of these tissues was measured in Warburg respirometers containing either 3 cc. of Ringer's solution with 0.1% glucose and buffered with phosphate or 2.7 cc. of horse serum and 0.3 cc. of Ringer's phosphate-glucose solution. In the experiments with serum the bicarbonate was removed by shaking with hydrochloric acid at pH 6, after which the pH was adjusted to about 7.4 with sodium hydroxide. All of the horse serum used was obtained from the same bleeding and was kept in sterile ampoules at 5° C. In the center cup of each flask was placed 0.3 cc. of 20% potassium hydroxide. The manometers were flushed with oxygen for 10 minutes and were shaken at a rate of 100 to 120 oscillations per minute at 38° C. Readings were taken at intervals of 10 minutes for 1 or 2 hours and then the pH of the substrate was tested. The slices of tissue were removed from the flasks, rinsed in distilled water, dried at 105° C. for 24 hours and weighed. There was, on the average, about 15 mg. of water-free tissue obtained from each flask. The results were calculated in the usual way—QO_2 = c.mm. O_2 consumed per hour per mg. dry weight of tissue. Except where stated otherwise, the values are based on the oxygen consumption during the 1st hour.

Thyroglobulin was prepared in the manner described by Canzanelli and Rapport.[1] It contained about 0.7% iodine. In dry form it remained active for several months. Preceding each experiment with thyroxin, the crystals were dissolved in saline with the aid of a very small amount of 1N sodium hydroxide. The thyrotropic hormones* used in these studies was found to have 50 Junkmann-Scholler units of thyroid activity per 1 cc. of solution.

The remaining details of the methods used are described in conjunction with the report of the results of the experiments.

Effect of Thyroglobulin. Thyroglobulin was found to increase the QO_2 of guinea pig and rat liver. In 6 of 7 experiments using horse serum as the substrate, the QO_2 of guinea pig liver was increased from 40 to 100%, as noted in Table 1. In the 4 experiments using rat liver and horse serum, the percentile increase in QO_2 varied from 30 to 37%. In each of 5 experiments using guinea pig or rat liver suspended in a medium of Ringer's phosphate-glucose solution, thyroglobulin produced a significant increase in the oxygen consumption (Table 1). In the 1 instance when the serum of a patient with hypometabolism, but not hypothyroidism, was used in conjunction with thyroglobulin, no increase in the QO_2 was observed. It is to be noted that no increase in oxygen consumption of diaphragm or kidney occurred during the 1st hour of incubation, but there was a significant increase in the 2nd hour.

On the basis of these results and the experiences of others, it is clear that thyroglobulin increases the QO_2 of many tissues. Therefore, it is important to know how this substance is related to the circulating hormone. Upon using a delicate test for thyroglobulin, Lerman[16] failed to demonstrate the presence of this substance in the blood stream, except after traumatization of the thyroid gland as during thyroidectomy. DeRobertis[6] postulated that a proteolytic enzymatic action in the thyroid gland leads to a disintegration of thyroglobulin, permitting the entrance of a smaller molecule, like thyroxin, into the blood stream. However, as illustrated by the following results as well as experiences of others,[3,4] it seems necessary for thyroxin to undergo

* Thyrotropic hormone (Antuitrin-T) was furnished through the courtesy of Dr. Oliver Kamm, Parke-Davis and Company, Detroit, Mich.

some process of activation before it can increase the rate of oxygen consumption of tissues.

EFFECT OF THYROXIN. Although thyroxin, when injected intravenously, causes a prompt and pronounced increase in the basal metabolic rate, many investigators have observed that this compound causes little or no increase in the QO_2 when it is added directly to tissues in Warburg respirometers.

TABLE 1.—EFFECT OF THYROGLOBULIN ON QO_2 OF GUINEA PIG AND RAT TISSUES

Substrate	Guinea pigs: Amount of thyroglobulin (mg.)	Guinea pigs: Increase QO_2 (%)	Rats: Amount of thyroglobulin (mg.)	Rats: Increase of QO_2 of QO_2
	Slices of liver		Slices of liver	
Horse serum	5.0	40	5.0	57
	5.0	0	5.0	30
	5.0*	100	10.0	38
	5.0*	93	10.0	50
	10.0	50		
	10.0	57		
	10.0	63		
Hypometabolism†	10.0	0	5.0	100
Ringer's phosphate-glucose	2.5	30	50.0‡	120
	10.0	44	5.0§	48¶
	100.0	55	5.0	111¶

* The thyroglobulin used in this experiment was prepared from a thyroid gland of man.
† The serum was obtained from a patient with hypometabolism but not hypothyroidism.
‡ Slices of kidney.
§ Slices of diaphragm.
¶ Oxygen consumption during the 2nd hour of incubating. No significant change in QO_2 took place during the 1st hour.

We found that the addition of thyroxin to liver slices caused no increase in the QO_2 during the 1st hour. Canzanelli, Guild and Rapport[3] found in most of their experiments that thyroxin had no stimulating effect. With thyroid tissue, Paal[21] found increases of 200% when it was suspended in serum and thyroxin for a period of 24 hours. Davis, DaCosta and Hastings[4] observed that thyroxin *in vitro* increased the tissue. Moreover, the increase in respiration of the frog heart did not occur until after several hours of incubation. Davis and Hastings[5] found that thyroxin increased the oxygen consumption of the excised limulus heart after incubation for 15 hours.

Rate of Activation of Thyroxin in Vivo. Some change probably takes place either in thyroxin or in body fluid or tissue before this compound can increase the rate of biologic oxidations. Such a change can take place within 6 hours *in vivo*, as shown in Figure 1. From each of 3 myxedematous patients serum was withdrawn for use as a control and then thyroxin in doses of 3, 5, or 12 mg. was administered intravenously. Four samples of serum from each of the 3 patients were obtained within the next 12 hours. Certain specimens of the serum added to slices of guinea pig liver in Warburg respirometers caused a distinct increase in the QO_2, the maximal response being obtained with serum withdrawn about 6 hours after the patients had received thyroxin. In the 2 patients who received the smaller doses of thyroxin, after 12 hours the effect of the serum was not much different from that obtained before these patients received thyroxin. Serum withdrawn 6 days after 1 patient had received 12 mg. of thyroxin yielded the same QO_2 as did pre-treatment serum. In a fourth myxedematous patient serum obtained 50 hours after the subject had been given 7 mg. of thyroxin gave the same results as serum obtained from this subject before treatment. These observations suggest that thyroxin does

become activated in the body within a few hours, but the site of activation is not known. Not much hyperactivity was demonstrated by the serum after 12 hours. The thyroid gland apparently did not participate in the reaction in these myxedematous patients since there was essentially no thyroid tissue present. The following experiments were conducted to determine whether thyrotropin, normal serum or liver tissue might affect the activation of thyroxin.

was added to 2.7 cc. of serum and slices of guinea pig liver. No calorigenic effect was observed, although in a similar experiment 0.1 mg. of thyroglobulin caused a 33% increase in QO_2.

Experiment III: Thyroxin + Antuitrin-T + serum were added to rat liver and the QO_2 was determined immediately thereafter. The rate of respiration was the same as without the hormones. The same results were obtained when guinea pig liver was used instead of rat liver.

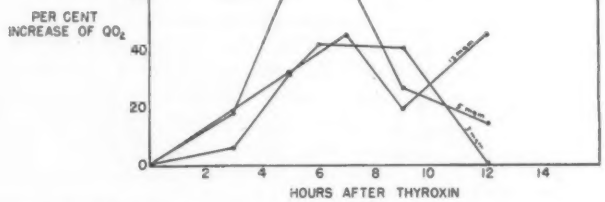

FIG. 1.—Note that serum obtained 3 hours after the injection of thyroxin caused a slight increase in QO_2 of liver slices, but the maximal effect was obtained after 6 to 9 hours. The larger the dosage of thyroxin the greater was the calorigenic action of the serum at 12 hours.

Is Thyroxin Activated by Serum and Thyrotropin? Experiment I: In this experiment the following solutions were measured out: (*a*) 0.9 cc. serum + 0.1 cc. (0.2 mg.) of thyroxin, (*b*) 0.9 cc. of Antuitrin-T + 0.1 cc. of thyroxin, (*c*) 0.5 cc. of Autuitrin-T + 0.4 cc. serum + 0.1 cc. thyroxin, (*d*) 0.9 cc. saline + 0.1 cc. of thyroxin, (*e*) 0.5 cc. of Antuitrin-T + 0.5 cc. of serum, and (*f*) 1 cc. of serum. The solutions were incubated at 38° C. for 5 hours and then 0.3 cc. of each was added to 2.7 cc. of horse serum containing slices of rat liver or heart. In no instance was thyroxin found to have a calorigenic effect.

Experiment II: One cc. (2 mg.) of thyroxin and 2 cc. of Antuitrin-T, pH 6.8 were incubated at room temperature for 48 hours. Then 0.3 cc. of the mixture

Is Thyroxin Activated by Serum and Liver? To 10 mg. of thyroxin, dissolved with 1 drop of normal sodium hydroxide, was added 10 cc. of serum. About 7.5 cc. of this mixture was incubated at 37° for 15 hours with 45 mg. of guinea pig liver slices and the other 2.5 cc. was incubated without liver. The liver slices were removed and the volume of the solution was increased 3 times with phosphate medium. An aliquot of 3 cc. was placed in respirometers in the presence of slices of fresh guinea pig liver. However, no calorigenic effect was observed.

Ten mg. of thyroxin, dissolved with 1 drop of sodium hydroxide, was added to 10 cc. of serum and an aliquot, 1.5 cc. was incubated with 21 mg. of guinea pig liver slices. Similar amounts of thyroxin-serum mixture without liver, and plain serum were incubated simultaneously at

37° for 48 hours. The liver tissue was removed and the solutions were diluted 10 times with phosphate medium and 3 cc. were used in the respirometers with liver slices. The QO_2 of the specimen incubated with liver was 300% greater than the 1 containing serum only.

In 6 similar experiments there was no increase in the QO_2 when the substrate contained thyroxin that had previously been incubated with serum (Table 2). However, when thyroxin was incubated with liver slices and serum, an increase in QO_2 occurred in 2 of the 6 experiments. No increase in QO_2 resulted when the incubation mixture consisted of serum and liver without thyroxin or when serum alone had been incubated for 48 hours. Moreover, when phosphate medium was incubated with or without thyroxin it led to no increase in QO_2.

Table 2.—Incubation of Thyroxin With Serum and Liver Tissue

Hours of incubation	Tissue (mg.) (dry weight)	QO_2 Control	Thyroxin + serum	Increase (%)	Thyroxin + serum + liver	Increase (%)
24	5.8	4.6 + 0.1	4.3 + 0.0	0	4.3 + 0.1	0
	9.7	5.6 + 0.1	5.4 + 0.1	0	5.5 + 0.1	0
	11.9	5.5 + 0.4	5.0 + 0.3	0	7.0 + 0.6	45
48	9.7	5.3 + 0.1	5.7 + 0.2	0	34.0 + 2.0	507
	7.2	5.1 + 0.3	5.0 + 0.1	0	5.6 + 0.2	0
	10.1	5.4 + 0.0	4.8 + 0.6	0	5.4 + 0.1	0

As to why thyroxin, incubated with liver and serum appeared to have become distinctly activated in 3 experiments and not in the other 4 is not known. It is possible that the liver and serum mixture might have the capacity of inactivating thyroxin as well as of activating it.

Effect of Thyrotropic Hormone. Two-tenths of 1 cc. of thyrotropic hormone (Antuitrin-T), added to serum containing slices of liver, heart, diaphragm or thyroid, caused no increase in the respective QO_2 (Table 3). There was no increase in QO_2 when thyroxin (0.2 mg.) and thyrotropin (0.2 cc.) were added to liver slices, nor when thyrotropin, thyroid tissue and liver tissue were incubated together. These observations are in accord with those of Canzanelli and Rapport,[2] who also found that when thyrotropin plus either thyroxin, thyroglobulin or diiodotyrosine were incubated with either thyroid or liver, the effects produced were additive ones of each of the test materials separately. These investigators concluded that the action of thyrotropic hormone on metabolism, through the thyroid, was not due to a specific effect on thyroxin, thyroglobulin or diiodotyrosine. Although thyrotropin stimulates thyroid cells *in vitro* as well as *in vivo*, the QO_2 of thyroid tissue is not necessarily proportional to the amount of hyperplasia that develops.[23]

Effect of Serum of Patients with Simmonds' Disease, Myxedema or Thyrotoxicosis. When normal horse serum was used as the substrate, the QO_2 of liver tissue was higher than when Ringer's phosphate-glucose was used (Table 4) However, there was no essential difference in the QO_2 of liver or heart whether the serum used was from a horse or a normal, thyrotoxic, myxedematous, or panhypopituitary individual. The respiration of diaphragm or pectoral muscle was the same with the serum of either a normal or thyrotoxic subject. The respiration of thyroid tissue varied in different experiments, but the results of individual tests demonstrated that the respiration was less in the presence of serum of patients with thyrotoxicosis than it was with serum of normal man or horse. Whether this decreased QO_2 was related to the increased amount of thyroid hormone in the serum is a matter of conjecture.

Biopsies were performed on the gastrocnemius muscles of 4 patients, 2 of whom had myxedema, 1 Simmonds' disease and

1 thyrotoxicosis. Only local anesthesia was used and care was taken to avoid getting novocaine in the muscle. Slices of myxedematous muscle were incubated with the sera of normal, thyrotoxic and myxedematous subjects. The QO_2 was essentially the same in each case. The muscle slices of the patients with Simmonds' disease or thyrotoxicosis had distinctly lower QO_2 values in the serum of patients with Simmonds' disease or the serum of thyrotoxic subjects than in normal serum.

each of the inhibitors was administered to rats, intraperitoneally in from 0.1 to 0.5 cc. of saline. Each of the rats weighed from 135 to 165 gm. Death occurred in 1 minute after 0.4 mg. of cyanide, after 4 minutes with 0.8 mg. of azide, after 18 minutes with 20 mg. of moniodoacetate, after 25 minutes with 200 mg. of malonate and after 46 minutes with 5 mg. of fluoride.

Three experiments were conducted with rats in which the inhibitors were given in the drinking water for 6 days or longer.

TABLE 3.—EFFECT OF THYROTROPIN (ANTUITRIN-T) ON THE QO_2 OF GUINEA PIG TISSUE

Tissue	No. experiments	Control	No. experiments	Thyrotropin (0.2 cc./flask)
Liver	22	7.6	3	7.6
Heart	17	5.9	3	5.9
Diaphragm	6	3.7	3	3.3
Thyroid	8	5.6	3	4.8

TABLE 4.—EFFECT OF TYPE SERUM ON QO_2 OF GUINEA PIG TISSUES

Tissue	Substrate	No. experiments	Average QO_2
Liver	R.P.G.*	4	4.2
	H.S.	22	7.6
	N.S.	13	7.5
	T.S.	14	8.5
	M.S.	5	7.3
	S.S.	4	6.8
Heart	H.S.	17	5.9
	N.S.	8	7.2
	T.S.	8	5.6
	M.S.	2	5.0
	S.S.	4	5.7
Diaphragm	H.S.	6	3.7
	N.S.	3	2.6
	T.S.	8	2.9
Pectoral muscle	T.S.	4	2.4
	T.S.	2	2.5

* R.P.G., Ringer's phosphate-glucose; H.S., horse serum; N.S., normal serum (man); T.S., serum of patients with thyrotoxicosis; M.S., serum of patients with myxedema; S.S., serum of patients with Simmonds' disease.

EFFECT OF ENZYME INHIBITORS. Five common enzyme inhibitors were studied. The experiments were divided into 2 main groups: the inhibitor was given in the drinking water of rats in 1 instance and in the other it was added to the substrate in Warburg respirometers.

In Vivo Studies. The dosages of the inhibitors were selected after conducting preliminary tests of the approximate lethal dosages, as illustrated by the following examples. The sodium salt of

Experiment I: Five groups of rats, with 3 in a group, each rat weighing from 130 to 190 gm., were given an inhibitor in the drinking water in the amounts listed in Table 5. After 6 days the basal metabolic rate was determined, the animals were killed with a blow on the head, and in some instances estimations of the QO_2 of the liver and heart were made.

On comparing the basal metabolic rates of these animals with those of animals of the same size and sex it was found

(Table 5) that the rate had increased in each group of rats, with the exception of the 1 receiving fluoride. With cyanide, azide and iodoacetate the increase was 50% or more. The QO_2 of liver slices was significantly decreased with cyanide and iodoacetate, but was essentially unchanged with azide and malonate, whereas the QO_2 of heart slices was decreased with malonate and iodoacetate, but increased with azide.

TABLE 5.—EFFECT OF INHIBITORS ON BASAL METABOLIC RATE AND QO_2 IN RATS

Inhibitor	Drinking waters (%)	B.M.R. (%)	QO_2 (%)	
			Liver	Heart
Cyanide	0.25	+60	−35	
Fluoride	1.25	0		
Azide	0.12	+50	0	+27
Malonate	0.40	+25	0	−28
Iodoacetate	10.00	+54	−24	−15

* Each inhibitor was in the form of its sodium salt.

TABLE 6.—EFFECT IN 10 DAYS OF INHIBITORS AND THYROTROPIN ON THE GROWTH AND BASAL METABOLIC RATE OF RATS AND THE QO_2 OF THEIR LIVER

Inhibitor	Dose* of inhibitor (mg./rat)	Weight gain (%)		Increase in B.M.R. (%)		Increase in QO_2 (%)	
		Inh.	Inh + TTH†	Inh.	Inh. + TTH	Inh.	Inh. + TTH
Cyanide	0.1	68	32	30	45	4	6
Fluoride	0.5	55	61	15	45	39	19
Azide	0.1	82	66	55	30	21	70
Iodoacetate	2.0	53	..	45			
Malonate	50.0	75	50	4	64	0	13

* Daily dose of inhibitor (inh.) given subcutaneously in 0.2 cc. of saline.
† TTH, thyrotropin (Antuitrin-T)—0.1 cc. given subcutaneously once daily.

Microscopic sections of the liver, muscle and thyroid of some of these animals revealed no abnormalities with the exception of slight hyperplasia of the thyroid in the animals receiving cyanide or malonate. In the latter there also was decreased colloid and greater vacuolization than normal.

Experiment II: In this experiment 18 rats, weighing from 33 to 40 gm. were divided into 9 groups. Once daily each animal in 5 groups was given, subcutaneously, 0.2 cc. of 1 of the 5 aforementioned inhibitors in concentrations listed in Table 6. Each of 4 other groups was given daily injections of thyrotropic hormone, 0.1 cc., and 1 of the inhibitors. After 10 days all rats had gained weight, but less rapidly than did normal control animals. The basal metabolic rate increased significantly in each group, the increase being greater in the ones which received thyrotropin plus an inhibitor, except in the group given azide. There was no decrease in the QO_2 in any of the 4 groups tested. In fact, there was an increase in the QO_2 of liver slices in the groups which received fluoride or azide.

Experiment III: This experiment was similar to the preceding one. There were 10 groups of rats with 2 animals in each group. These rats had an average initial weight of about 75 gm. They were given the same inhibitors and thyrotropin in the same dosage as in the previous experiment. After 8 and 14 days there was no decrease of the basal metabolism, but there was not as much increase as in the previous experiment. Again there was a distinct inhibition of weight gain.

Sections of the thyroid and liver of each of the animals were examined microscopically. There were no remarkable abnormalities in the liver and no hyperplasia of the thyroid except in the groups receiving thyrotropin.

It is clear that with the doses of inhibitors used no decreased basal metabolic rate was produced in rats. However, that some inhibitory effect probably took place

is indicated by the decreased QO_2 that was observed in some instances. The increase in the intact animal was probably related to a variability in the response of different tissues to the inhibitors with an inefficient metabolism resulting.

In Vitro Studies. The effects of cyanide, fluoride, malonate, azide and iodoacetate on the QO_2 of slices of liver, heart and diaphragm of hyperthyroid guinea pigs were tested. The hyperthyroidism was produced by the injection of thyrotropin daily for several days preceding the test. The concentration of the inhibitors used in the Warburg vessels was either 0.02 or 0.04 M. Iodoacetate was also tested in concentrations of 0.002 and 0.004 M. In 1 experiment 50 mg. of thyroglobulin was added to slices of liver of normal animals and the inhibitory effect of iodoacetate was tested.

The amount of inhibition of cyanide was about 85%, of iodoacetate 40%, of fluoride 35% and of malonate and azide 30%. Similar degrees of inhibition were observed with slices of liver, heart and diaphragm of normal guinea pigs.

These observations are in keeping with those of McEachern,[18] who concluded that cyanide, fluoride and moniodoacetic acid reduced the respiration of hyperthyroid tissues, but did not affect the fundamental mechanism which makes an increased supply of oxygen necessary to the organism. Gordon and Heming[11] found that fluoride or cyanide caused the same percentage decrease in QO_2 of both normal and hyperthyroid liver slices, and malonate produced equal QO_2 values. These investigators found that malonate caused marked inhibition in the respiration of hyperthyroid rat diaphragm but no change in the normal tissue.

Discussion. Neither the precise structure of the thyroid hormone nor its site of action has been demonstrated. However, sufficient data have been accumulated to permit reasonable tentative hypotheses. Since (*a*) proteolytic action on thyroglobulin antecedes its liberation from the thyroid gland;[6] (*b*) thyroglobulin apparently does not usually circulate in the blood stream;[16] (*c*) thyroxin, unlike thyroglobulin, does not exert a calorigenic effect on tissue slices for several hours; and (*d*) thyroxin polypeptide promotes a distinct stimulation of the basal metabolic rate whether given orally or intravenously,[19] it is possible that thyroxin exerts most of its calorigenic action in the form of a peptide. If thyroxin polypeptide is the active form of the thyroid hormone, it may be asked where is the site of conjugation when thyroxin is administered to a thyroidless individual. Apparently the liver possesses this capacity; whether there are other sites is not known. Thyrotropin caused no activation of thyroxin.

It is of especial interest that some of the common inhibitors of respiratory enzymes, when given to intact animals, did not produce a lowering of the basal metabolic rate, but promoted hypermetabolism. Since the same compounds, when added to slices of tissues, caused a pronounced inhibition of oxygen consumption, it seems reasonable to conclude that with the dosages used there was a variation in the response of the tissues, the inefficiency in function of some tissues leading to hyperfunction of others. The situation might be compared to animals with marked thiamine deficiency in which the QO_2 of certain tissues is reduced, but the basal metabolic rate is increased. These observations raise the question, which has often been considered in the past, as to whether hyperthyroidism is a compensatory reaction to an altered metabolic state in the tissues.[2,3]

Summary. Studies were made of the effects of thyroglobulin, thyroxin and thyrotropin on the oxygen consumption of tissues of rats, guinea pigs and patients with alterations in thyroid function. Investigations of the effects on these tissues of serum of normal subjects and of patients with thyrotoxicosis, myxedema or Simmonds' disease were also made. Studies of the effects of common respiratory enzyme inhibitors were made in normal and hyperthyroid animals.

Although thyroglobulin usually caused a prompt increase in QO_2 when added to slices of tissue, thyroxin rarely had any such effect, either alone or in conjunction with thyrotropin. In a few instances, when thyroxin was incubated with liver slices and serum for 1 or 2 days and then the solution was added to fresh tissue, a distinct increase in QO_2 resulted. The fact that other similar experiments demonstrated no effect with thyroxin suggested that the same medium might activate and inactivate thyroxin.

In 1 series of experiments thyroxin was injected, intravenously, into 3 patients with myxedema and 4 specimens of serum were obtained during the next 12 hours. In each patient the serum acquired the capacity to increase the QO_2 of slices of guinea pig liver. The maximal effect was obtained about 6 hours after the injection of thyroxin and thereafter it tended to disappear. Thyrotropin was not found to increase the QO_2 of slices of liver, heart, diaphragm or thyroid. When serum of a normal man or horse was used as a substrate with slices of tissue a higher QO_2 was obtained than when Ringer's phosphate-glucose solution was used. There was no essential difference in the QO_2 of heart or liver tissues whether the serum used was from a normal, thyrotoxic, myxedematous or panhypopituitary individual.

Whether slices of muscle of myxedematous patients were incubated with sera of normal, thyrotoxic or myxedematous subjects, the QO_2 values were essentially the same.

The sodium salts of cyanide, fluoride, azide, malonate and iodoacetate, administered to rats for several days, caused an increase in the basal metabolic rate and an inhibition of growth. The QO_2 values of liver slices were increased in most instances, but decreased in a few. However, each of the compounds, when added to Warburg respirometers containing slices of liver, heart or diaphragm from normal or hyperthyroid animals, caused a distinct decrease in QO_2.

Further studies on the site and mechanism of action of the thyroid hormone are in progress.

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VAGOTOMY FOR PEPTIC ULCER

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During the past 20 years there have been many changes in viewpoint with regard to the therapy of peptic ulcer by surgical means. The most common operations performed years ago for the treatment of duodenal ulcer were simple gastro-enterostomy and pyloroplasty. In the early 30's an increasing number of partial gastrectomies were performed, and until recent years partial gastrectomy has been the operation of choice for the treatment of duodenal ulcer. The transition in popularity from gastro-enterostomy to partial gastrectomy was due primarily to the high incidence of gastrojejunal ulcers following gastro-enterostomy. The removal of a fair portion of the acid-producing area of the stomach tended to reduce the number of jejunal ulcers, and while the incidence is lower following adequate partial gastrectomy, this latter procedure is not insurance against their occurrence. Many have objected to partial gastrectomy on the basis that it is a mutilating operation which sacrifices a considerable amount of the stomach.

In 1943 Dragstedt and his associates[16] performed bilateral resection of the vagus nerves as a means of decreasing the excess secretion of acid seen in ulcer patients. Since practically all methods of treatment of duodenal ulcer are based on control of acid in the stomach or its diversion from the duodenum, resection of the vagus nerves has been received with enthusiasm, not only because it is well known that stimulation of the vagus nerve increases acidity in the stomach and resection of these nerves causes a decrease in acid secretion, but also because of the simplicity of the procedure. As might be expected, bilateral resection of the vagus nerve below the lower border of the bifurcation of the trachea is not a new procedure. This operation has been frequently proposed and there is a record of the operation having been performed in 1911.[20] Since this time the operation has been performed for gastric crisis as well as for peptic ulcer, but as a method of therapy for either disease the operation was discontinued. Experimental work has

been carried on in relation to the effect of the vagus on gastric acidity since 1904.[14]

In 1900 Jaboulay[33] extirpated the celiac plexus and Mingazzini[47] divided the posterior nerve roots intradurally for relief of gastric crises in tabes dorsalis. The object of this operation was the control of pain. It was not until Foerster[21] developed a procedure similar to Mingazzini's that Exner, in 1911,[20] attempted to simplify the Foerster operation, by dividing the vagi subdiaphragmatically in a manner almost identical to the Dragstedt[15] procedure of today. He noted atony of the stomach and performed a gastrostomy over a tube passed through the pylorus into the duodenum to correct this condition. Later he performed a gastro-enterostomy in addition to the vagotomy. Bircher, in 1920,[7] reported favorably on vagotomy, but his indication for the operation, like Exner's, seemed to have been tabes or any "obscure gastropathy" as only 1 of his cases had ulcer. Latarjet[40] first reported on this procedure in 1922. He sectioned the vagal filaments in the abdomen after the main trunks had divided and applied the procedure to tabes, peptic ulcer and "obscure gastropathy." He makes the same claims for the procedure as are made today. He felt it was indicated in cases of peptic ulcer without obstruction and in more than half of his cases he added gastro-enterostomy. He remarked that following the operation alimentation was normal, the patients gained weight, had an immediate sense of well-being, and considered themselves cured. In all, Latarjet,[40] Wertheimer,[41] Pauchet[52] and Gianolla[24] reported 59 cases, in 18 of which they had done vagotomy alone. Giordano,[25] Stierlin[60] and undoubtedly others have also used the procedure but the record of their work is not now accessible.

Borchers,[8] in 1921, and Koennecke,[37] in 1922, reviewed the work on vagotomy for the preceding 11 years. Although they accepted the seemingly favorable results obtained, they objected to the operation on the theoretical basis that cutting the nerve supply to the stomach, gall bladder, small bowel and half of the colon for disease of the stomach and first part of the duodenum was not justified.

Laignel-Lavastine[39] reviewed the literature in 1924 and commented favorably on the future of vagotomy, and Eiselberg,[19] in 1925, predicted that the more radical procedure of gastrectomy would some day be replaced by vagotomy.

Schiassi,[56] in 1925, reporting on 26 cases of duodenal ulcer, had done vagotomy alone in 11 cases, and vagotomy plus gastro-enterostomy in 15 cases. He did the Latarjet procedure which consisted of division of the vagus nerves below the diaphragm and added to it an incision which circumcised the outer layers of the gastric wall at about the junction of the proximal and middle thirds. He seemed enthusiastic about this procedure also. Pieri,[53] in 1932, reported 14 cases in which infradiaphragmatic vagotomy was performed. He described sectioning both main trunks beneath the diaphragm for peptic ulcer. At the time of his report he had done 6 vagotomies without gastro-enterostomy and stated that he doubted the necessity for the latter procedure.

We are unable to find any record of an unfavorable report concerning this operation. Pieri[53] has reported that secretion and motility in some of his cases returned to normal within a matter of months, but he does not offer the results of these studies as argument against the procedure. We could find no report of a recurrent ulcer following vagus resection. We might suppose that knowledge of the operation was not widespread, as Pieri in 1932 credits only Exner and Giordano with having previously performed bilateral vagotomy.

At about this time, however, the procedure of gastro-enterostomy and pyloroplasty were being superseded by gastrectomy and the surgical attention seems from 1920 on to have been focused on this operation with its many variations to the exclusion of vagotomy. Even those who in that day considered gastrectomy a "mutilating, unphysiologic procedure" were

not raising their voices in defense of vagotomy and the operation received no mention in standard surgical textbooks of the time.

C. H. Mayo,[44] in 1928, did several selective vagotomies evidently for the lesion of pylorospasm. He sectioned the gastrohepatic omentum above the distal stomach and proximal duodenum and in that way deprived these tissues of their vagal supply.

It is to be pointed out in consideration of the older attempts at vagotomy, that the type of operation was quite varied and in most instances there is doubt that the entire vagus innervation of the stomach was resected. Surely attempts at resection of filaments on or within the stomach wall cannot be considered as complete vagotomy since in some instances the resection was performed in the mid-portion of the stomach and did not resect the nerve high enough to cause much effect upon acid secretion. There is but 1 report which appears to us to have approached the problem in a manner which might be considered as adequate. Pieri[53] performed subdiaphragmatic vagotomy by exposing the lower end of the esophagus and sectioning the 2 main vagal trunks. This procedure appears to be similar and just as complete as that done today. There is no question that the basic concept was that resection of the vagus nerve might vary the course of a peptic ulcer. However, there is no doubt that the effects of vagotomy were not clearly understood until the careful work of Dragstedt and his associates[16] in 1943.

Since atropine, which has had an important and time-honored place in the treatment of peptic ulcer, acts by paralyzing the vagal end-organ, one might say that there has been a wealth of clinical experience with vagotomy. Rokitansky,[55a] in 1841, however, seems to have been the first to describe ulcer of the stomach as "due to morbid condition of the vagus and to the extreme acidification of the gastric juice." This idea has been expressed many times since by Arndt,[1] Beneke,[6] Hart,[29] Hoffman,[31] Roessle,[55] von Winiwarter,[67] and others. Some of the opinions or studies have been made on the basis of observed association between cerebral neoplasm or birth injury to cerebrum, on the one hand, and ulceration of the stomach or melena neonatorum, on the other. Wilks,[71] in 1889, in questioning the rôle of the vagus, stated that ulcer of the stomach could be considered neurotrophic just as we have neurotrophic corneal ulcer, and von Bergmann,[65] in 1913, emphasized that the parasympathetic system is disordered in ulcer; that these patients respond more readily to pilocarpine; and that the long-continued use of atropine will therefore either cure or ameliorate the disease.

Cushing,[13] in 1932, again advanced the theory of the neurogenic origin of peptic ulcer. He makes the interesting point that only man of all animals develops ulcer spontaneously and that the incidence of the disease is increasing with the increasing stress of modern living. This coincidence is striking in itself; but, as evidence of central nervous system involvement in peptic ulcer, he reported his unusual experience of having 3 patients die in the immediate postoperative period of perforated peptic ulcer following the removal of cerebellar tumors during which there had been long-continued use of electrodesiccation. Also, in autopsy material, he had noticed ulceration of the gastric mucosa in 2 cases of cerebral tumors in other locations. There were 2 cases of malignant hypertension which had gastric ulceration, in 1 of which death was due to perforation of the ulcer. He reported a case of duodenal ulcer in a 9 year old female child who had had a cerebral tumor removed and subsequent deep Roentgen ray therapy. One amazing instance was that of a patient with symptoms of cerebellar tumor who was treated by deep Roentgen ray therapy with relief of symptoms. He returned later with recurrence of cerebellar symptoms and duodenal ulcer. On resuming Roentgen ray therapy, the symptoms of both lesions disappeared. This entire sequence of events was repeated again when the patient for a second

time was admitted with symptoms of both lesions.

Very recently Strassman[61] studied the relation of acute mucosal hemorrhages and ulcers of the gastro-intestinal tract to intracranial lesions in a large number of autopsies. He reports that in 26 cases of acute hemorrhagic ulcerations and 30 cases of softenings and perforation of the esophagus, stomach and duodenum, all but 2 were associated with intracranial lesions..

In 1942, Wolf and Wolff[72] studied a patient with a chronic gastric fistula and observed that in situations involving anxiety, hostility and resentment there was a "profound and prolonged hyperemia, hypermotility and hypersecretion."

Thornton, Storer and Dragstedt[63] studied the night secretion of several groups of patients with the following results:

No. cases	Type of case	Average 12 hour night secretion, cc.	Free acidity in clinical units
9	Carcinoma of stomach	261	0–21
5	Carcinoma of colon	238	0–18
6	Gall bladder disease	385	0–13
10	Peptic ulcer	821	47*

* Average clinical units.

In the duodenal ulcer group, the values after vagotomy dropped to an average night secretion of 385 cc. with free acid values of 0 to 13 clinical units. They regard these as truly impressive data and feel that since the patients were asleep and therefore not subject to stimulation by food or psychic factors, the night volume must be due to abnormally great secretory tonus in the vagus nerves.

Dragstedt and his associates have shown that the stimulation of gastric secretion by insulin hypoglycemia, as described by Hollander,[33] dependent as it is upon central nervous system stimulation, is abolished by vagotomy. They studied, during sleep, gastric tonicity and hunger contractions of the stomach by means of a balloon attached to a Miller-Abbott tube; and, while there is increased tonus and increased frequency and amplitude of hunger contractions in peptic ulcer, there was a definite decrease following vagotomy. They have shown that caffeine and histamine stimulation, acting on the peripheral neuroglandular mechanism of the stomach, have a pharmacologic action not altered by vagotomy.

Moore, Chapman, Schulz and Jones[50] make the point that the efficacy of atropine in the treatment of peptic ulcer has been due to the fact that it alters the permeability of the cell to acetylcholine, thus blocking parasympathetic impulses at the end-organ. With bilateral vagotomy, then, one has a complete and permanent atropinization of the area. They showed with barium an increase in initial emptying time of the stomach of from 1½ to 15 to 20 minutes; and an increase in complete emptying time of the stomach of from 2 to 2½ to 12 to 24 hours. They showed a lessening of peristaltic activity and of large gastric contractions, but no change in gall bladder emptying time. They studied sensation in the lower esophagus and stomach to balloon distention but found no change. Dragstedt[15] has, shortly after vagotomy and while the patient feels entirely well, surreptitiously introduced weak solutions of hydrochloric acid into the stomach and reproduced ulcer pain. These 2 facts indicate that sensory fibers to the stomach do not travel in the vagi.

An interesting experience of Moore[49] was reported in 1946. He did vagotomy on a patient who had had a gastric resection without removal of the antrum. Following vagotomy, the patient was not clinically well, but became so when his side-tracked antrum was later removed. This is significant in that it tends to confirm Edkin's[18] work on gastric hormone and the considerable clinical experience with recurrent difficulties when the antrum is retained. According to Babkin[2] there

is a triple mechanism for gastric secretion. The first chemical, induced by such substances as histamine and alcohol; a second hormonal, and a third or psychic one which is the only mechanism interfered with by vagotomy. The symptom complex of peptic ulcer following section of both vagi may be explained on either a chemical or hormonal basis.

Dragstedt[15] has pointed out that Carlson has proved a continuous basal secretion of gastric juice. This basal secretion is augmented by the taste, sight and odor of food. Section of the vagus nerves does not entirely eliminate gastric secretion as this can still be stimulated by the presence of food within the stomach and the liberation of gastric hormone; also, the chemical phase of gastric secretion is not altered as histamine and caffeine act independently of the nerve mechanism.

There is a wealth of experimental work in support of the rôle of the vagus nerve in peptic ulcer. Schiff,[57] in 1867, Brown-Sequard,[9] in 1875, and Ebstein,[17] in 1874, have shown ulceration of gastric or duodenal mucosa to follow central nervous system stimulation by either cauterization or chromic acid injection. von Preuschen[66] and Pomorski[54] confirmed these findings. Mogilnitzky,[48] in 1925, and Burdenko,[10] in 1926, have shown the production of chronic ulceration of gastric or duodenal mucosa due to central nervous system stimulation, and this work has been confirmed by Keller[35] in this country.

Westphal,[69] in 1926, produced ulcers in cats, rabbits, dogs and guinea pigs by the subcutaneous injection of pilocarpine. Light, Bishop and Kendall[43] have shown that very small amounts of pituitrin or pilocarpine injected intraventricularly will produce ulcers of the stomach and duodenum. Beattie[3] has shown that electrical stimulation of the central nervous system will produce vagal stimulation and ulceration of the mucosa of the stomach or duodenum which will be abolished by vagal section. Keppich,[36] in 1921, and Stahnke,[59] in 1924, reported the production of typical peptic ulceration by continuous electrical stimulation of the vagus nerves. There was hypermotility, hypersecretion and ultimate erosion of the mucous membrane.

The vagal nerve supply to the stomach has been bilaterally sectioned in animals by many workers. Donati,[14] in 1904, sectioned both vagi and reported no ulceration of the mucosa. This was repeated by Lichtenbelt[42] in 1912, Greggio[27] in 1917 and Koennecke[37] in 1922. Beazell and Ivy,[5] in 1936, used bilateral vagal section in rabbits to study the effect of trauma in ulcer production since vagotomy produces stasis. In 1915 Chiari[11] produced chemical block of the vagi with atropine and reported diminished gastric secretion and marked suppression of hydrochloric acid secretion.

From 1919 to 1922, Latarjet[40] did experimental work on animals in which he denervated the stomach of its vagal filaments and found that there were no harmful effects on the animals and that gastric motility was still present. There was, however, definite hypotonicity, delay in emptying and dilatation. He found that for 3 years this state of affairs continued. He noted that such a dog (post-vagotomy) required 7 hours to empty his stomach, whereas only 2 were required before. In this animal, there was also diminished hydrochloric acid secretion and no trophic lesions.

In 1929, Hartzell[30] sectioned the vagus nerve in dogs both intra-abdominally and transthoracically. He found a marked reduction in both the free and total acid, and noted that incomplete section of the vagus nerves caused little or no postoperative secretory change. Vanzant,[64] in 1932, reported further studies on these same dogs. Their gastric acidity had returned to normal and reëxamination of the operative sites in 3 dogs showed that the nerves had not regenerated. There was still a slight delay in emptying and a slightly subnormal response to histamine. Pieri and Lapenna[53] showed the same changes in the human being.

In 1931, Beaver and Mann,[4] working with the Mann-Williamson preparation in

dogs reported failure of the usual peptic ulcer formation when vagotomy was done. The rate of occurrence in a sympathectomized group was the same as in the control group.

Shapiro and Berg,[58] in 1932, created Pavlow pouches and did gastrojejunostomies in a series of dogs. Before vagotomy the acid in the pouch showed 100 to 120 clinical units, and after vagotomy only 40 to 50. The main gastric values ranged from 85 to 100 clinical units and fell to 40 to 50 units after vagotomy. There was also marked skin irritation around the pouch opening before vagotomy, which cleared after vagotomy. In 4 to 5 weeks, however, the acid values returned to normal and the skin irritation from the pouch discharge returned.

One may say now that for those cases of peptic ulcer in which the psychic phase of gastric secretion is greatly increased (due to central nervous system disturbance brought to bear on the gastric glands through the intermediary of the vagus nerve) section of the vagi is rational. Hyperemia of the mucosa seems to be associated with hypersecretion. There is evidence, both clinical and experimental, that section of the vagi at the esophageal plexus and distally does no harm, within short subsequent periods of time at least; but there is considerable evidence that the resulting hypoacidity and hypomotility may not be permanent.

Fulton,[22] in his discussion of the vagus nerve, describes the synaptic junctions in the wall of the stomach in the ganglia of the myenteric and submucosal plexuses. He states that the parasympathetic activity promotes digestion and aids in the passage of food through the gut. When stimulated, peristalsis is increased, the sphincters relaxed, and the production of gastric juices including salivary and pancreatic are stimulated. Digestion, however, can proceed adequately following bilateral section of the vagi at the level of the diaphragm, and bilateral section of the splanchnic nerves. The preoperative level of tonus and peristaltic activity is soon reëstablished.

The anatomy of the vagus nerves is not so well established. According to Gray,[26] the vagus nerve, which has the most extensive course and distribution of any of the cranial nerves, contains somatic, motor and sensory fibers and parasympathetic efferent fibers. On the distal end of the esophagus, the vagi form a plexus, tend to reform into 2 main trunks and, passing through the diaphragm, break up into small filaments along the lesser curvature. We may schematically represent this as in Figure 1.[23] It is the parasympathetic efferent fibers, arising from the dorsal nucleus of the vagus, which principally concern us. These are preganglionic fibers to the thoracic and abdominal viscera. They end in small ganglia in or near the organ and postganglionic fibers carry the impulse to the end-organ. In the abdomen, the effects of the parasympathetic fibers to the stomach and small intestine are augmentory; the sympathetic inhibitory. The removal of the effects of 1 set of fibers, as by section, results as a rule in the effects of the other set seeming more prominent. This indicates that each type of fiber exerts a constant or tonic action and suggests that the 2 effects are delicately balanced one against the other.

Walters, Bradley, Small and Wilson[68] made dissections in more than 100 autopsy cases. They found that while the vagi do, in varying patterns, tend to form 2 main trunks on the lower esophagus, in 8% of the cases the fibers took such a course that it would have been very difficult to completely section them below the diaphragm. Miller and Davis[46] studied the vagus nerves in autopsy specimens and concluded that the variations in the course of the fibers are such that section should be done transthoracically.

Jackson[34] in a study of the vagus in 26 cadavers showed the varied courses of the vagus both on the lower esophagus and on the stomach itself. He also reports a clinical application of this knowledge in that the branch from the posterior vagus

which goes to the celiac plexus may be preserved by leaving the main trunk and the celiac division intact and dividing the remaining segments of the gastric branches of the posterior nerve alone. This he calls "selective vagal resection." Dragstedt[15] has noted fibers traveling in the wall of the esophagus itself.

Since 1943, when Dragstedt[15] first reported on this procedure, the clinical literature on vagotomy is fast growing. His performance of this operation was preceded by many years of work on gastric physiology and in his reports on this procedure he has at some length given his reasons for considering this a rational

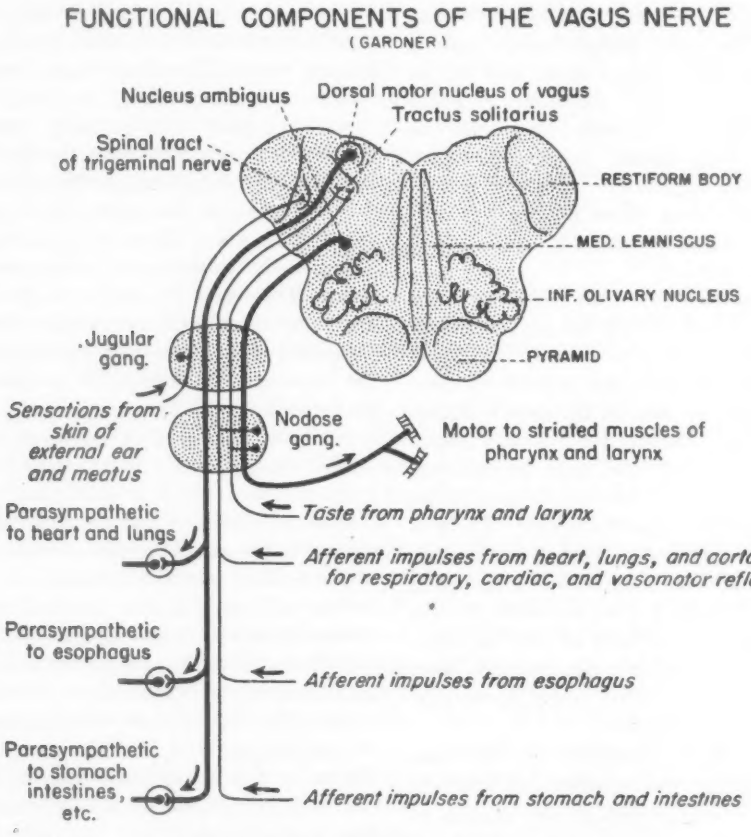
FUNCTIONAL COMPONENTS OF THE VAGUS NERVE
(GARDNER)
Nucleus ambiguus
Dorsal motor nucleus of vagus
Tractus solitarius
Spinal tract of trigeminal nerve
RESTIFORM BODY
MED. LEMNISCUS
INF. OLIVARY NUCLEUS
PYRAMID
Jugular gang.
Sensations from skin of external ear and meatus
Nodose gang.
Motor to striated muscles of pharynx and larynx
Taste from pharynx and larynx
Parasympathetic to heart and lungs
Afferent impulses from heart, lungs, and aorta for respiratory, cardiac, and vasomotor reflexes
Parasympathetic to esophagus
Afferent impulses from esophagus
Parasympathetic to stomach intestines, etc.
Afferent impulses from stomach and intestines

FIG. 1.—Functional components of the vagus nerve.

We are now in the process of studying the exact degree of variation of the course of the vagus through the posterior mediastinum and shall report on this later. In the operation of vagotomy, an attempt is made to section completely nerves, the anatomy of which is not constant, and in so doing we of necessity disturb an existing delicate balance of nervous control of the gastro-intestinal tract by the sympathetic and parasympathetic nervous system.

procedure. His first 40 cases were done by the transthoracic route which he abandoned because of complaint of pain along the course of the affected intercostal nerve. This we have noted in our series and shall comment on it later. Moore, Chapman, Schulz and Jones[50] have also reported on 50 cases done by the transthoracic route. Grimson *et al.*[28] have reported on 40 cases done transthoracically.

Our first 15 cases were done transthorac-

ically for the following reasons. The procedure was suggested only in proven cases of duodenal ulcer or post-gastrectomy complications in which we felt nothing would be gained by seeing the lesions. All had the typical peptic ulcer syndrome with definite Roentgen ray findings and high free acid so that we felt the diagnosis was well established. They represented medical failures or surgical failures in both coöperative and uncoöperative patients. Further, we not only felt that complete resection of the vagus nerve could be more easily accomplished transthoracically, but we were interested in the appraisal of vagotomy alone as a method of treatment, and felt that appraisal of its efficiency when combined with gastro-enterostomy might be misleading.

The advantages of transthoracic vagotomy are the ease with which the vagus can be sectioned and the fact that it may be employed shortly after acute perforation. We feel that complete section, which is important, is more nearly possible in every case by this route. The disadvantage is that the lesion is not seen unless one opens the diaphragm, which we have not done, but which has been done by Moore[50] routinely in at least his first 12 cases. It offers decided disadvantages if it is advisable to see or feel the lesion and would not be employed by choice if one were confronted with the necessity of also doing gastro-enterostomy for obstruction. We have, however, used transthoracic vagotomy only for those cases of peptic ulcer in which the diagnosis had been established by repeated Roentgen ray examination and substantiated by incidents of previous hemorrhage, perforation or obstruction. In most cases we felt we would learn no more about the patient by examination of the ulcer *in situ*.

In our hands section of the vagus is easier transthoracically and offers better opportunity for complete section, and we reserve the abdominal route for those unusual cases in which there is question of obstruction or associated pathology.

Dragstedt has reported on another 100 cases done by the transabdominal route, and Walters *et al.*[68] also have reported on large series of cases done by the subdiaphragmatic approach. Crile[12] has recently reported 77 cases done by the subdiaphragmatic route. Undoubtedly there will in a few more years be reports of much larger series done by both methods and with longer periods of postoperative observation.

We have done abdominal vagotomy in 7 cases. Four gastro-enterostomies were done in these cases, but in retrospect we think 2 were not necessary.

The indications as described for vagotomy are similar in all recent reports. It is being done primarily for duodenal ulcer for which medical management has failed, so that the patient either continues to have his symptom complex or during course of active treatment has developed such complications as hemorrhage, obstruction or perforation. Secondly, it is being done for surgical failures such as jejunal ulcer following either gastro-enterostomy or gastric resection. A few cases of vagotomy have been reported for gastric ulcer, but these have been done for very particular reasons. Of our 32 cases the ulcer was duodenal in 27 cases, gastric in 2 cases, jejunal in 4 cases and 1 case had gastro-jejunocolic fistula. The duration of the peptic ulcer syndrome in these cases varied from 1 month to 24 years, and the average was 8 years. The 2 cases of gastric ulcer were admitted to the hospital for acute perforation, which at time of gastrorrhaphy presented no unusual findings and had pathologic confirmation of ulcer by biopsy. Their transthoracic vagotomies were done 9 and 17 days following the gastrorrhaphies. These cases were done too recently for comment, but they are being followed very closely.

We feel that 1 perforation of duodenal ulcer is sufficient reason for vagotomy and where there is no obstruction following simple repair, we proceed during the next week or 2 to do a transthoracic vagotomy and then discharge the patient to the follow-up clinic.

It was necessary in all cases to treat postoperative gastric atony rather vigorously, but in only 1 case did we feel gastroenterostomy might be advisable, and that patient refused operation. In all cases we have kept the patients on intermittent gastric suction for from 2 to 10 days; intermittent, as we at the same time insisted upon early ambulation. We have used tetra-ethyl ammonium bromide in 2 cases. This should relax the pyloric sphincter if the obstruction is due to an imbalance of nervous control. We felt that the drug was of benefit in 1 case. In the second case, we could see no effect on the pylorus under fluoroscopy and discontinued the drug.

It has seemed strange to us that other chest procedures in which thoracotomy incisions are used cause so very much less intercostal pain than does vagotomy; and this fact must be related to the nervous disposition of the ulcer patient. We have had less complaint than has been reported in other series, possibly due to our extensive use of intercostal block, but it can always be elicited by question. In our later cases we have either crushed or sectioned the intercostal nerve and feel that this is a good procedure.

We have also employed intercostal block on the left from the sixth to the tenth ribs very freely, using about 5 cm. of 1% novocaine to each nerve, and repeating the injection as symptoms dictated, sometimes as often as every 5 hours for 2 to 5 days. Such nerve blocks allow earlier return to full function of the left chest.

The 1 case which we felt had become obstructed left the hospital on the 5th postoperative day and was not seen again for 8 weeks. We feel that his obstruction was organic only on the basis of long-continued gastric dilatation and that this could have been prevented by closer observation and decompression. We very seriously doubt the necessity for subjecting the patient to the added hazard of gastro-enterostomy in any case which does not have prevagotomy obstruction. Several of our cases have had Roentgen ray diagnosis of grossly deformed duodenal bulbs, but still have had no more than ordinary postoperative difficulty.

Very little mention has been made in the recent literature concerning anesthesia for vagotomy. Transthoracic section should not be attempted without excellent anesthetic supervision. With proper anesthesia the operation is technically easier to perform transthoracically than abdominally. We have had no fear of vago-vagal reflex since our Anesthesia Staff feels that it seldom, if ever, happens under ether anesthesia.[62] We have used no precautions concerning injection of the nerve before section; nor have we transplanted and fixed the proximal end to the pleura after section as Moore and Dragstedt have done; nor have we attempted to repleuralize the esophageal bed. This simplifies the operation to the point where one may expose through the left pleural sac from 2 to 4 inches of the esophagus under controlled respiration anesthesia (using ether as the anesthetic agent), and locate the vagus nerves and the lower portion of the esophageal plexus in order to do a complete section.

Complete resection of both vagi is the essential of the operation. The gastric secretory glands must be made inaccessible to central nervous system influences. Hartzell[30] has shown the necessity for this by pointing out that partial section does not give quantitative reduction of acid secretion. Vanzant[64] has shown return to normal acid secretion in dogs 2 years after section. Shapiro and Berg[58] show an even more rapid return to normal in their animals. Pieri[53] has reported in his patients, in some of whom he had sectioned only the left vagus, that "following the operation there was a lowering of the hydrochloric acid and of pepsin, a lowering more conspicuous in the cases in which the section was bilateral, but that postoperatively the hydrochloric acid and pepsin rose progressively and in some cases reached or surpassed the preoperative figures." He thought this was to be understood on the basis of "the mechanism of functional

compensation, obscure but sure, that takes place in the vegetative nervous system." Our series of cases is neither great enough nor the follow-up studies long enough for us to offer information on these points.

White and Smithwick,[70] commenting on this, think that the return of function could be due to (1) the high degree of automaticity of the digestive process so that it can be regulated by the intramural plexus, (2) the presence of mixed components of the splanchnic and vagal trunks, or (3) the fact that preganglionic fibers have such an extraordinary power of regeneration. The second point does not explain failure of ulcer formation in peripheral stimulation of the sympathetic nor the sharp contrast in results using the Mann-Williamson preparation in dogs with and without sympathetic and vagal section. The third has been disproven by both Vanzant[64] and Dragstedt.[15] The latter claims that the vagal trunks do not regenerate even when immediately resutured. The automaticity characteristic must explain the return of acid production to normal.

If vagotomy failed of successful establishment as a worthwhile therapy on the European continent, we feel that return of some acid secretion post-vagotomy on the basis of automaticity was not the factor, but incomplete section of the nerves instead. We have reproduced a chart from McCrae's[45] article in 1925 which roughly illustrates their operative attack upon the vagi (Fig. 2). Incomplete section is most likely to happen in the Latarjet procedure, less likely in the Exner or Dragstedt procedures where the lower esophagus is well mobilized from below, but we feel least likely to happen when 3 or 4 inches of the esophagus is exposed through the chest. To explain the early good clinical results upon which the European surgeons based their enthusiasm, one need only postulate physiologic interruption in fibers which, though missed, were put on stretch or subjected to pressure as in blunt dissection, and then resumed their function weeks to months later. No clinical test of the completeness of section, such as the insulin hypoglycemia stimulation, would disclose the presence of such unsectioned but nonfunctioning fibers. We have not used this test in our recent postoperative cases for

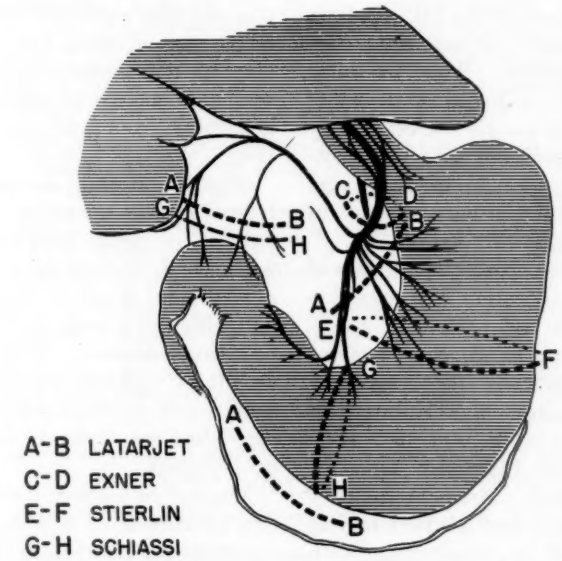

FIG. 2.—Diagram illustrating earlier operative methods of performing vagotomy.

this reason, but feel that, if after 6 to 12 months our patients should begin having chronic dyspepsia, the test would then apply.

We have also used the night secretion test of Dragstedt[15] as a test of hypertonicity of the vagus. The test is open to 2 inaccuracies in that an uncoöperative patient may drink fluids or any patient may lose fluid through the pylorus. The test gives quite variable results if used in patients who have had gastro-enterostomy or resection. We have also noted that following vagotomy one may obtain a high night secretion (in 1 case 1200 cc.) and that one may also obtain free HCl readings of as high as 40° and still have a negative hypoglycemic reaction. This we must explain on the basis of Babkin's[2] theory of the triple phase of gastric secretion only one of which is interfered with by vagotomy. It is then possible to have high acid secretion still on either the basis of chemical or hormonal stimulation.

It is because of such discrepancies and the fact that the operation was once discontinued that we feel such cautions as those of Lahey[38] apply. He compares our present-day enthusiasm for vagotomy with that once mistakenly exhibited for gastro-enterostomy and total thyroidectomy. He prefers vagotomy now for those cases in which gastro-enterostomy will not be necessary and for postsurgical complications, and in conjunction with subtotal gastrectomy for duodenal ulcer.

We have had 1 recurrence of ulcer following vagotomy. This patient had duodenal ulcer for 10 years and was seen in the sanitorium where he was being treated for advanced bilateral pulmonary tuberculosis. Only 1 routine gastric analysis was done preoperatively and that showed high free HCl acid. A transthoracic vagotomy was done following which, despite some difficulty with gastric atony, he was symptomatically well for 16 days. He then had a recurrence of typical chronic dyspepsia with epigastric pain which continued in varying severity for several months. Finally there was an attack of very severe epigastric pain and some degree of vascular collapse, and he expired 48 hours later. Autopsy showed an ulcer on the lesser curvature bordering on the esophago-gastric junction with perforation and generalized peritonitis. The duodenal ulcer was present but appeared inactive. It measured 3 cm. in greatest diameter, while the gastric ulcer was 2 cm. in diameter. Unfortunately there was such tissue destruction from infection and postmortem autolysis that examination of the lower esophagus for incomplete section of the vagi was unsatisfactory. Since the surgeon felt he had done complete section, one can only speculate on such factors as intramural fibers of the vagus or gastric ulcer on some basis other than neurogenic such as hormonal or chemical or histamine absorption from pulmonary tissue destruction.

Almost uniformly, however, our patients following this operation claim they are well. Their peptic ulcer symptom complex with which they were so familiar disappeared, and none of them confused his difficulties of gastric atony with his preoperative disease. They have gained weight on unrestricted diet and have in some cases resumed smoking and drinking—pleasures which had previously been denied them.

Moore,[51] in his recent edition of "Modern Treatment of Syphilis," says of this operation for gastric crisis in tabes dorsalis that more experience is "urgently desirable." We feel that the same may be said of peptic ulcer of the duodenum and for postgastrectomy complications of peptic ulcer with the possible exception of those few cases in which there is retained antrum.

The experience with resection of the vagus nerve in the treatment of duodenal ulcer appears very heartening indeed. However, it is of importance to point out that except for the frequent sporadic use of this procedure in the past, the operation has actually been performed only over the past 4 years. When one remembers the glowing reports from the use of gastro-

enterostomy for the treatment of duodenal ulcer, our inclination is to be cautious about final results. At this stage it is impossible to state what the status of vagotomy will be 10 years from now. The results so far in our clinic have been impressive. If the procedure provides even temporary help to those individuals who have developed jejunal ulcers after what appears to have been an adequate gastrectomy, the operation will be a decided advance providing no serious permanent sequelæ result from the operation. We have noted nothing which would indicate that serious sequelæ result. It has been well emphasized in many of the articles on vagotomy that this procedure should be carried out only after a very careful evaluation of the patient and the patient who had a vagotomy should have a very careful follow-up for evaluation of results.

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OPHTHALMOLOGY

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OCULAR LESIONS IN BRUCELLOSIS

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Determination of the etiology of iritis, uveitis and choroiditis, especially of the chronic or recurrent type, is an almost daily problem which confronts the ophthalmologist and his consultants. The clinical appearance of some of the lesions is sufficiently characteristic to warrant a presumptive diagnosis of the cause. In many instances, however, the lesions are of non-specific type and clues to the etiology must be sought through the history of the patient, systemic examination and laboratory tests. And even if the clinical appearance is suggestive of a certain etiology, confirmatory findings are desirable before a definite diagnosis is established. Unless extensive studies are carried out, which may at times seem almost too exhaustive, the cause of many cases will go undetermined. Examinations carried out by Woods and Guyton[15] included general physical examination, laboratory examinations of urine, hemocytology and blood chemistry, serologic tests for syphilis, intracutaneous tests for tuberculin sensitivity, roentgenologic examination of the chest, search for foci of infection, gonococcus complement fixation tests, agglutination tests for brucellosis, biopsies of lymph glands, estimation of serum albumin and globulin, roentgenograms of the hands and feet, specia bacteriologic examinations, sensitivity studies, examination of spinal fluid and neutralization tests for toxoplasma, and yet the cause remained undetermined in 22 of 200 cases.

Twenty-five or 30 years ago, focal infection was quite generally accepted as the cause of those lesions of the uveal tract which could not be assigned definitely to syphilis, tuberculosis or bacterial metastasis in the course of an active infection. Even in the 1941 series of Guyton and Woods,[8] in which more complete studies were carried out, the cause was stated to be either syphilis, tuberculosis or focal infection in 86% of 562 cases. In the 1943 series of Woods and Guyton,[15] this percentage had dropped to 61. The percentage of cases assigned to focal infection had dropped from 26 in the 1941 series to 6 in the 1943 series. In the 1943 series, 7.5% were attributed to sarcoidosis and 7.5% to brucellosis as against 0.5% and 0.4% in the 1941 series.

It is well known that metastatic involvement of the uveal tract can occur in the course of streptococcic, staphylococcic, pneumococcic, meningococcic and other septicemias. It would be logical to assume that similar inflammations of the eye might occur in acute cases of Brucellosis when the organisms are present in the blood stream. This assumption seems to be supported by experimental and clinical evidence. Fabyan[5] stated, in 1912, that, following intra-abdominal or subcutaneous inoculations, *Bacillus abortus* caused lesions in guinea pigs of a practically constant and most remarkable character. The acute changes appeared usually between the 3rd and 6th week

after inoculation and continued over a period of 10 to 20 weeks accompanied by fever. The disease tended to final recovery; but the animal might die from rupture of the spleen or as the result of emaciation and exhaustion. Three of his animals developed blindness in 1 or both eyes as the result of opacity of the cornea. Histologically, the sclera, choroid and lacrimal glands of the diseased eyes showed areas of infiltration, chiefly of lymphoid elements. Some typical tubercles were seen and also intracellular bacilli. Orloff,[12] in 1928, reported on the histologic examination of the eyes of 19 guinea pigs that developed lesions of the cornea and lens during the course of Malta fever. These animals were among a group of 200 affected in an epidemic. The eyes showed circumcorneal injection, clouding of the cornea, either centrally or in the form of a gray infiltrate fading out from the margin to the center, hyperemia of the iris with posterior synechiæ or with the pupil filled with grayish exudate. Histologically, the changes in the cornea varied from mild cellular infiltration with degeneration of the epithelium and endothelium to thick cellular infiltration with formation of new vessels resembling the lesions of syphilitic parenchymatous keratitis. Diffuse and focal infiltration with lymphoid and epithelioid cells and endovasculitis and perivasculitis was found in the iris, the ciliary body and the anterior part of the choroid. These changes were most definite and extensive in the ciliary body. In the retina, degeneration of the ganglion cells and edema of the outer nuclear layer and of the layer of rods and cones were noted. Orloff thought that the lesions were produced partly through the action of toxins and partly by direct invasion by the organisms. In 1939, Burky, Thompson and Zepp[4] presented strong evidence that infection with *Brucella abortus* is a cause of periodic ophthalmia in horses which is similar to recurrent endogenous uveitis in humans. In the course of their experiments, they demonstrated that 1 of the strains of brucella that they had recovered would, on intravenous injection into rabbits or on direct inoculation into the eye, produce a generalized keratouveitis similar clinically to severe tuberculous lesions and resembling histologically periodic ophthalmia in horses and chronic recurrent intraocular inflammation in humans.

Most of the reports of ocular lesions occurring in association with brucellosis have dealt with cases in the acute phase of the disease. Thus, in 1939, Green[6] collected the reports of 23 authors (cases of Aurand, Aubaret and Roger, Villard and Pech, Bergmark, Bingel and Jacobstiel, Cannavo, Cohen Boulakia, Godwin, Lemaire, Lundsgaard, Levy and Uzan, Aubaret and Guillot, Madievskaya, Roger, Villard and Viallefont and Temple, Rizzo, Mossa, DeJong, McCullagh and Clodfelter, Rutherford, Carranza, Roger, and Sella). In all the cases, the brucellosis was in an acute or at most in a subacute phase. The optic nerves were involved in 14 cases, in the form of optic neuritis in 9, in the form of choked disk in 4, and in 1 of Rutherford's cases, possibly as the result of subarachnoid hemorrhage rather than of the brucella infection itself. Meningitis was stated to be present in 4 of the cases with optic neuritis and in all of the cases with choked disks. Paralyses of ocular muscles were described in 6 instances, all with meningitis. Involvement of the uveal tract was reported in 7 cases and of the retina in 1 case. Brucella organisms were cultured from the blood in 3 of the cases with uveitis and in the case with septic retinitis. In the discussion of Green's paper, Snell[14] reported a case of central retinitis and Blake[3] the recurrence of a dendritic ulcer of the cornea, which occurred in each instance during the active stage of brucellosis. A study of these reports still leaves open the question whether iritis, uveitis or choroiditis can develop as the result of brucellosis in its chronic or latent phase.

Green[6] reported at the same time 4 original cases. In 2 of these, the brucella infection was in an acute phase apparently.

One of these patients had central retinochoroiditis and the other optic neuritis. A third patient had, during the chronic or latent stage of brucellosis, recurrences of a phlyctenular keratoconjunctivitis, the first attack of which had occurred during the acute stage of the infection. In the fourth patient, who had active central choroiditis, there was no history of an acute illness and the diagnosis was based on a strongly positive reaction to a cutaneous test for *Brucella abortus*. In 1943, Green[7] presented a case of chronic progressive kerato-iritis which he believed to be due to chronic brucellosis. It was his opinion that adequate laboratory tests for brucellosis should be made routinely in every chronic inflammatory lesion of the uveal tract and that, if the diagnosis were established, prompt energetic treatment with a brucella vaccine might check the progress of the disease. Berens,[2] on the other hand, was inclined to think that ocular brucellosis must be quite rare. He stated that skin tests with *Brucella abortus* antigen were made on 39 patients with inflammatory lesions of the eye, mainly involvements of the uveal tract. A positive reaction was obtained in only 1 patient with uveitis. Agglutination tests for *Brucella abortus* were done on 43 patients and for *Brucella melitensis* on 5 patients. All were negative.

Reed and Goldfain[13] stated that ocular symptoms and signs may occur in an individual with chronic brucellosis. They reported 3 cases of recurrent iritis in all of which the skin tests were positive and agglutination tests were positive in dilutions of 1:200. They included in their report also a case of recurrent ulcer of the cornea in which the skin test was positive but the agglutination negative.

Harris[9] reported 3 cases of recurrent iritis and 1 case of recurrent keratitis which he attributed to brucellosis. One of the patients with iritis had run a low grade fever for 5 years. An agglutination test was negative, but the cutaneous reaction was positive and the phagocytic index was low. Later, this patient developed meningo-encephalitis and died. Brucella had been isolated from the stool of another patient with iritis 1 year before observation. At the time of observation, an agglutination test was negative but an intradermal test with brucella antigen was strongly positive and focal reactions occurred in the choroid after the intradermal test and after the subcutaneous injection of 0.1 cc. of mixed brucella filtrate. A woman had had recurrent keratoconjunctivitis for 4 years. An agglutination test was negative, but the cutaneous reaction was positive and the phagocytic index was low. Clinical recovery was complete after 4 months treatment with *Brucella abortus* vaccine. The phagocytic index was high and there was no recurrence during an 18 month period of observation. In a case of uveitis reported by Agin,[1] the diagnosis of brucellosis was based on a strongly positive skin test. In spite of vaccine therapy, the uveitis terminated in phthisis bulbi. The eye was enucleated, but the results of histologic examination were not available at the time of the report.

Jones and Norris[10] reported 1 case of acute uveitis and 1 of conjunctivitis occurring in individuals who had positive skin tests for brucellosis. They mentioned also some interesting observations, the interpretation of which is not quite clear. They mapped the tangent screen fields of 111 persons some of whom had visual complaints, some of whom had only physical complaints, and some of whom were included in a routine study of individuals who came in contact with certain chemicals. Ninety-two (81.4%) of these individuals showed widening of the normal angioscotomas (Evans). Of the 92, 75 (81.5%) gave positive skin reactions indicative of brucellosis. Of 19 persons in whom the angioscotomas were of normal width, only 3 (15.7%) gave similar positive skin reactions.

In their paper on "The Rôle of Sarcoid and of Brucellosis in Uveitis," Woods and Guyton[15] present an analysis and evaluation of 15 cases which they attributed to

brucellosis. Seven of the patients had recurrent iritis; 5 had generalized uveitis; 3 had only lesions in the choroid, "1 or more elevated moderately circumscribed exudates with little surrounding reaction or generalized subretinal edema." The uveitis was of granulomatous type in 8 cases and of non-granulomatous type in 7. It was recurrent in 11 of the 15 cases. The cornea was involved in 2 cases. An additional case of nummular keratitis is mentioned as occurring in a patient with chronic brucellosis and the question is raised as to the possible etiologic rôle of brucellosis in nummular keratitis. One case of uveitis progressed to phthisis bulbi and the eye was enucleated. Histologic examination revealed "a non-specific uveitis with several conspicuous lymphoid nodules, a picture quite suggestive of that of periodic ophthalmia in horses." All of the patients gave a history of ingestion of raw milk or raw milk products and most of them had had unexplained fever previously. Only 1 patient had a prolonged low grade fever during the period of observation. Hence the patients must have been in the chronic or healed phase of the infection. Agglutination tests against *Brucella suis* and *Brucella abortus* antigens of living organisms were positive in dilutions of 1:20 to 1:320 in 13 of the 15 cases. In 1 patient, agglutination tests were negative but the complement fixation reaction was strongly positive. In the remaining patient, both the agglutination and the complement fixation tests were negative, but "the cutaneous sensitivity test was violently positive and there were no other etiologic factors." A cutaneous sensitivity test was done on only 5 patients; it was positive in 4 and negative in 1.

It is generally recognized that it is very difficult to establish a positive diagnosis of chronic brucellosis. In most instances, the diagnosis must be taken to be presumptive only. The brucella organisms cannot be cultured from the blood in chronic cases. The agglutination titer is high in the acute stage but drops as the case becomes chronic and may even fall to zero while the patient still has a low grade fever. The complement fixation reaction is not thought to be satisfactory for diagnostic purposes because it is not sufficiently specific. Woods and Guyton[15] checked the complement fixation reactions of 76 patients for both brucella and gonococci; 21 patients were positive to brucella but 18 of the 21 were positive to gonococci also. Woods and Guyton[15] seem to favor the employment of agglutination tests for diagnostic purposes and do not place much reliance on the cutaneous sensitivity tests or the opsonocytophagic index. However, Green,[7] Harris,[9] and McGinty and Gambrell[11] seem to favor the combined appraisal of the cutaneous sensitivity test and the opsonocytophagic index, since they think that the agglutination reaction is apt to be negative in the majority of cases of chronic brucellosis.

Harris[9] thinks that the agglutination test is of diagnostic significance only when it is positive in dilutions of 1:80 or higher. Harris[9] states that the intradermal test for brucellosis is comparable in all respects to the tuberculin test. He agrees with McGinty and Gambrell[11] that a positive reaction indicates only that the patient has been infected at some time and that it gives no information as to the present status of the infection. By determining the phagocytic activity of the leukocytes towards brucella organisms, however, it is possible to determine whether infection is still present or the patient is immune. The skin test may be made with a heat-killed suspension of brucella organisms in saline or with brucellergin, a suspensoid of nucleoprotein from brucella cells. McGinty and Gambrell[11] prefer brucellergin since it is more standardized and causes less systemic reaction and less local necrosis. Also it interferes less with the agglutination and opsonocytophagic tests. Harris[9] prefers the use of 0.1 cc. of a heat-killed vaccine prepared from the abortus strain only. Harris[9] thinks that the opsonocytophagic

test is of value for 2 reasons: (1) to determine the degree of specific resistance of the patient to brucella organisms as an aid to interpretation of the cutaneous reaction; and (2) for comparison with future tests if the patient is given vaccine therapy.

It would appear that the treatment of acute and chronic brucellosis is not entirely standardized or satisfactory. Among methods of treatment are mentioned sulfonamides, artificial fever, intravenous typhoid vaccine, human immune or convalescent serum, antiserum produced by inoculation of animals with live organisms, brucella vaccines and brucellin. For the acute stage, Harris[9] suggests sulfadiazine or sulfathiazole, transfusions of immune or non-immune blood, Foshay's antiserum. He thinks that artificial fever is of value only occasionally. For the treatment of chronic brucellosis, Harris[9] prefers the intramuscular administration of a vaccine made from the abortus strain alone. Among 400 patients so treated, satisfactory results were obtained in 75%, good results in between 15 and 20%. The treatment failed in about 5 to 10%. He stated that the only commercially available vaccines obtainable at the time his paper was written (1944) were prepared from mixed strains of brucella and might give undue reactions.

Finally, in attempting to evaluate the rôle played by chronic brucellosis in the etiology of acute, chronic and recurrent iritis, choroiditis and uveitis, it would seem to be logical to accept the views of Woods and Guyton.[15] A positive diagnosis cannot be made since it is not possible to isolate the organism and therapy is not sufficiently adequate to constitute a therapeutic test. However, "the accumulated evidence indicates brucellosis is probably an etiologic factor in uveitis, and it may be quite an important one." Positive agglutination and sensitivity reactions to brucella in a patient with uveitis have probably essentially the same significance in the diagnosis of etiology as positive reactions to tuberculin.

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BOOK REVIEWS AND NOTICES

HUMAN EMBRYOLOGY. By BRADLEY M. PATTEN, Prof. of Anatomy in the Univ. of Michigan Medical School. Pp. 776; 446 ills., 53 in color. Phila.: Blakiston, 1946. Price, $7.00.

THIS new volume is an excellent textbook of embryology for the medical student. The author is eminently qualified to write on this subject, being both a teacher of medical students and writer of well-known texts on the embryology of the pig and the chick. In this book he has aimed at presenting only those aspects of this tremendous subject that have a direct bearing on human development, normal or abnormal. The book begins with an introductory chapter on general embryology, its place in science and, in particular, its place in medicine. This is followed by chapters on the reproductive organs and the sexual cycle, followed by the early development of the embryo, the establishment of the organ systems and the general growth and development of the body as a whole. After a chapter on monsters and teratology there are 11 chapters describing the development of each of the organ systems. Each portion is presented so that it emphasizes its relation with the other subjects of the medical curriculum.

The book is well written, the illustrations are excellent and the Bibliography most complete. It is printed on good paper and is well bound. Besides being of great value for students, physicians in all branches will find this book most helpful as a reference text. It can be most highly recommended.

W. S.

CHARLES - EDOUARD BROWN - SEQUARD, a 19TH CENTURY NEUROLOGIST AND ENDOCRINOLOGIST. By J. M. D. OLMSTED, PH.D., D.SC., Prof. of Physiology, Univ. of California. Pp. 253; 2 ills. Balt.: The Johns Hopkins Press, 1946; London: Humphrey Milford Oxford Univ. Press, 1946. Price, $3.00.

THIS monograph records the 8th series of Hideyo Noguchi Lectures of the Johns Hopkins Institute of Medicine. The many references to Brown-Sequard's medical writings, the biographic references and a good Index make this a scholarly source of information about the man and his work.

To this something has been added. The reader will be delighted by an excellent biography. The hero, in spite of some faults, captures one's attention and affection. His time spent in the United States will arouse the interest of American readers. In the last analysis it is Dr. Olmsted's literary skill which makes this a book to read for pleasure, a rare quality in medical writing. F. L.

SURGICAL PATHOLOGY. By WILLIAM BOYD. M.D., M.R.C.P. (EDIN.), F.R.C.P., (LOND.), LL.D., Prof. of Pathology, Univ. of Toronto. 6th ed. Pp. 858; 530 ills., 22 in color. Phila. and London: Saunders, 1947. Price, $10.00.

THIS edition remains an outstanding contribution to the field of surgical pathology, and is an excellent source of information to the pathologist and student. Several additions have been made, and newer concepts of pathologic processes are included. Sections on fibrous dysplasia and pinealoma add to the completeness of the book. Recent theories concerning eosinophilic granuloma are considered. The subject of cystosarcoma phallydes is perhaps too rapidly dismissed. There is an interesting new addition of congenital cardiac defects that are amenable to surgical treatment. I. Z.

TUBERCULOSIS AS IT COMES AND GOES. By EDWARD W. HAYES, M.D., A.C.P., Assoc. Prof. of Tuberculosis, College of Medical Evangelists, Los Angeles; Medical Director and Physician-in-Charge of the Maryknoll Sisters Sanatorium, the Keane Sanatorium, and the Lair Sanatorium, Monrovia, Calif. 2nd ed. Pp. 209; 34 figs. Springfield, Ill.: Charles C Thomas, 1947. Price, $3.75.

THIS edition of a book written for patients has increased the space devoted to tuberculin testing and case finding, in line with im-

proved methods instituted since the publication of the 1st edition in 1943. In some instances, diagrammatic figures have been added to complete case histories, and other cases have been included. Other additions include the Dock theory on rest, expansion of the chapters on surgery, a brief mention of rehabilitation, and a section on "Suggestions to Visitors," the latter by Laurence de Rycke, Ph.D. Relatively little attention is devoted to drug therapy, and no information is given to orient patients with respect to the newer methods of medical treatment of this disease, which have been widely publicized in recent years. A pleasing format and the increased use of bold-face type to accomplish emphasis add to the attractiveness of the new edition. E. L.

CIRUGIA OCULAR. By H. ARRUGA. Pp. 888; 1218 ills., 119 in color. Barcelona and Buenos Aires, Salvat Editores, S. A., 1946. No price given.

THIS is a complete textbook on the surgery of the eye, of over 800 pages, magnificently illustrated. The illustrations are so extraordinarily beautiful that even if one cannot read Spanish, the author's intent is made clear. Since most operative techniques can be made clearer by illustrations than by the written word, the language difficulty should not prevent anyone from buying this book. The author is well recognized in this country as an authority on retinal detachment and because of his many original contributions to all phases of ophthalmic surgery. He and the publishers are to be congratulated on this magnificent volume. F. A.

PHILOSOPHY AND MEDICINE IN ANCIENT GREECE. By W. H. S. JONES, LITT.D., F.B.A., Supplements to the *Bulletin of the History of Medicine*. No. 8. Pp. 100. Balt.: Johns Hopkins Press, 1946. Price, $2.00.

THIS supplement of the *Bulletin* is the result of 8 years labor by the well-known Greek scholar and translator of the works of Hippocrates (Loeb Classical Series), aided by F. M. Comford until the latter's death. Section 1 (25 pages) considers briefly the Pre-Hippocratics, Plato and the Hippocratic Corpus. Section 2 is an essay on Hypothesis in Greek thought and on Philosophy and Medical Etiquette. Section 3, by far the largest part of the study, is devoted to the Hippocratic "Ancient Medicine." Following an interesting Introduction, are given the Greek text, a translation with comments and several pages of additional notes. Indications of erudition are obvious in this production; the style, like that of the original Greek, is clear and terse. The translation differs but little from that of the Loeb volume. This Supplement will be received as further evidence of Dr. Sigerist's wisdom in organizing this series of Supplements and of the Institute's success in productive research in medical history. E. K.

GYNECOLOGY WITH A SECTION ON FEMALE UROLOGY. By LAWRENCE R. WHARTON, PH.D., M.D., Asst. Prof. of Gynecology, The Johns Hopkins Medical School. 2nd ed. Pp. 1027; 479 ills. Phila. and London: Saunders, 1947. Price, $10.00.

THE author has admirably incorporated a 247 page section on female urology into a clearly written textbook of gynecology. The presentation is concise and largely limited to fundamentals.

This edition has been improved over the 1st by 35 more illustrations and by the rewriting and rearrangement of a number of sections to clarify and expand original subject material and to include recent advances. New chapters on gynecologic diagnosis and embryology, and one by Dr. C. R. Prince on "Water Cystoscopy" deserve special mention. G. H.

HARVEY CUSHING. By JOHN F. FULTON. Pp. 754; 99 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, $5.00.

FOR many more than his numerous admirers Harvey Cushing was, in Sherrington's words, "the most distinguished surgeon in this country, if not in the world"—this coming at a time when American surgery was forging most rapidly ahead to a leading world position. As this study well demonstrates, he was also a zealous educator, the book itself owing something, as will be seen below, to his desire to help medical students. Cushing was highly skilful as an operator and still more distinguished as a student of disease and of ways of recognizing and overcoming it. His artistic and literary gifts were of a high order; he was a discriminating bibliophile with a long enough purse to

satisfy his desire to bring together a notable library of important rare medical books The history of medicine was to him a valuable discipline as well as a lifelong field of interest. Such a versatility of eminence offers great opportunity to a biographer, if adding correspondingly to the responsibility of his task. There should be general agreement, however, that it has been well carried out by Dr. Fulton, who was early delegated as Cushing's literary executor, and has been at work on this biography, except for serious interruption by the war, since shortly after Cushing's death. Also a distinguished student of the nervous system, educator, bibliophile and book collector, medical historian and experienced writer, and on the same Faculty with Cushing for several years before his retirement, Fulton was an ideal man for the job.

The volume is constructed on much the same lines as Cushing's own biography of Osler, except that being in one volume the details of his clinical work, especially in its technical phases, have been purposely curtailed. The same chronologic approach has been followed, with H. C.'s age conveniently repeated on each recto and the month and year on each verso. The same kind of material is included as in the Osler volumes —with numerous excerpts from Cushing's voluminous diary and letters. The book is well embellished with close to 100 illustrations, many fortunately being of Cushing's attractive pen and ink sketches. The present volume does not suffer by comparison with the Osler—a big compliment, truly. We are indeed fortunate that two such distinguished medical men should live on in these intimate, simple yet revealing biographies.

Cushing's intense, scintillating character shines through almost every page, with its valleys as well as its heights, the latter presented without show, the former without evasion. For instance, when depressed from overwork at Harvard, he writes: "Able to do no studying for some time . . . suicide about only alternative . . ." The episode of his accusatory letter to Dandy about the acoustic nerve tumor work, which provoked a lifelong bitterness, is frankly met—though in a sympathetic way that helps the reader to a better understanding of this complex character. As one might expect, there are not a few similar incidents, for this is not an account of a placid life. More frequent opportunity arises, however, to let events illustrate the thoughtfully generous side of Cushing's nature; his many kindly deeds to assistants and students and those in want or distress; the Oslers' reaction to his presence at the deathbed of their son, Revere—these are but a few of the many instances given with obvious zest by a biographer who evidently has tried not to be carried away by his great admiration for his subject.

Aware that a biography was to be prepared, Cushing characteristically made provision in his will for a subvention, which has permitted preparation of this handsome as well as adequate volume at extremely low cost for these days of costly publishing. The medical world at large, as well as the medical students whom he is said to have had primarily in mind, should profit accordingly. E. K.

PRINCIPLES OF THE CONTACT LENS. By H. TREISSMAN and E. A. PLAICE. Pp. 88; 40 ills. London: Henry Kimpton, 1946. Price 10s/6d net.

This is a clear and concise evaluation of contact lenses and should be of value to all those who prescribe them. There is an excellent chapter on the physiologic optics of contact lenses with a comparison of the optical merits of spectacle lenses as compared to contact lenses. The methods employed in fitting and testing contact lenses are adequately described. The factors are mentioned which militate against tolerance in wearing contact lenses, but unfortunately no solution has as yet been found for those patients who develop corneal edema.

F. A.

CLINICAL METHODS OF NEURO-OPHTHALMOLOGIC EXAMINATION. By ALFRED KESTENBAUM. Pp. 400; 65 ills.; 20 tables. New York: Grune & Stratton, 1946. Price, $6.75.

THIS is an excellent book and is highly recommended for neurologists and neurosurgeons, as well as ophthalmologists. The first 5 chapters deal with the physiology and pathology of the optic pathways. In the first chapter, a review is given of the anatomy of the optic pathway; the second

deals with disturbances in the visual fields; the next 3 treat disorders of the various portions of the optic pathway; namely, the optic nerve, the chiasm and the retrochiasmal portions of the optic pathway. The sections on chiasmal lesions and retrochiasmal lesions are especially well done. Following this, are chapters on paralysis of the ocular muscles and supranuclear paralyses, nystagmus and disturbances of the symmetrical eye movements, such as convergence and divergence. Chapter 10 deals with pupillary abnormalities and disturbances of accommodation. Chapter 11 includes alterations in the palpebral fissure and a group of miscellaneous disturbances, such as trigeminous nerve affections and the Kayser-Fleisher ring in pseudosclerosis. The final chapter is concerned with functional disturbances.

The general style of the book is good and the illustrations, though diagrammatic, are excellent. The only possible fault that can be found is the inclusion, probably for completeness, of a number of tests for differentiating the site of lesions in the optic pathways, which are generally conceded to have little clinical value. In practically every instance, however, the author has been careful to point this out. It is the most practical book on neuro-ophthalmology which has so far appeared in English. F. A.

URGENT SURGERY. By JULIUS L. SPIVACK, M.D., LL.D., Associate Professor of Surgery, University of Illinois College of Medicine; Corresponding Member Mexican Academy of Surgery; Senior Attending Surgeon, Columbus Memorial Hospital, Chicago; Attending Surgeon, Oak Forest Infirmary. Vol. I. Pp. 714; 572 ills., 14 in color. Springfield, Ill.: Charles C Thomas, 1946. Price, $10.50.

THE purpose of this volume is not clear to the Reviewer nor does the title seem justifiable. The surgeon who is to do most of the procedures described in the text must be a trained operator, and there is little that he can learn from this book. The "casual operator" referred to, as for example when simple closure of a perforated ulcer is discussed, should certainly not be encouraged to undertake the "urgent" 2-stage perineal operation for imperforate anus or an internal choledochoduodenostomy. Splenopexy under any circumstances can hardly be regarded as urgent nor can operations for cysts of the spleen.

In this day of rapid transportation it is inconceivable that a child with pyloric stenosis cannot be taken to a competent surgeon who has had basic surgical training and who, if he wishes to review the steps of an uncommon operation, will go to a source book containing more anatomic and physiologic detail than this one.

This volume therefore cannot be warmly recommended nor the title condoned in the light of the contents chosen. I. R.

THE EYE MANIFESTATIONS OF INTERNAL DISEASE. By I. S. TASSMAN. Pp. 614; 243 ills., 24 in color. St. Louis: C. V. Mosby, 1946. Price, $10.00.

THIS is a well-written and readable book on medical ophthalmology. Although in no sense an exhaustive treatise, it covers the field well and includes good references to the literature. F. A.

VICTORY OVER PAIN. By VICTOR ROBINSON, M.D. Pp. 338; 47 ills. New York: Henry Schuman, 1946. Price, $3.50.

THIS is a readable, instructive, lucid and entertaining history of anesthesia. The author tells a stirring tale and makes many of the great characters of the 19th century live again.

The publishers state "we are all aware that scientific advances have reached a point where they dominate the lives and destiny of everyone. With this awareness has come a natural desire to understand more fully the rôle and impact of science on our everyday life." Anesthesia is one of these "scientific advances," and Dr. Robinson portrays in fascinating detail the rôle that American, English, Scottish, French, German and Russian medical circles have played in the development of this science. Anesthesia is regarded by all thinking people as one of the major contributions of man to his fellow. This book recounts the hazards and disappointments of research, the numerous failures to recognize the significance of new observations and the struggles for fame and fortune that followed the introduction of general anesthesia. Numerous anecdotes and many letters make this one of the most

entertaining histories that the Reviewer has read. It can be recommended without hesitation to all who are interested in the progress of medicine, be they laymen or physicians.

P. D.

OCULOREFRACTIVE CYCLOPEDIA AND DICTIONARY. By THOMAS G. ATKINSON, M.D., B.S.C. 3rd ed. Pp. 388. Chicago: Professional Press, 1944. Price, $5.00.

THIS is a dictionary of ophthalmologic terms in which some of the terms are merely defined and others are expanded into encyclopedic references. This makes such a discrepancy in the value of the book for reference that it partially destroys its usefulness. Under Ptosis for instance, there is merely a sentence defining the condition, whereas 11 pages are given to the heading, Psychology of Vision. The book does contain a considerable amount of interesting material which is not readily available in other sources, but it is very uneven.

F. A.

PENICILLIN: ITS PRACTICAL APPLICATION. By 30 British Practitioners and Researchers. Edited by SIR ALEXANDER FLEMING, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor of Bacteriology in the University of London. Pp. 380; 59 figs. Philadelphia: Blakiston, 1946. Price, $7.00.

THE name of Fleming attached to a book on Penicillin is enough to arouse great expectations. As far as the historical background, general principles, and the bacteriologic aspects are concerned, these expectations will be realized; the 2 chapters on these topics were contributed by Sir Alexander himself. The chapters on Chemistry and Manufacture, Pharmacy, Pharmacology, and Methods of Administration are also well done and reasonably adequate, as of the spring of 1946 in Great Britain. These, with Fleming's 2 chapters, occupy the first 104 pages and constitute the General Section. The remaining 21 chapters comprise the Clinical Section and are written by 24 specialists, including a dentist and a veterinarian who contribute appropriate discussions. As would be expected, there is considerable overlapping and unevenness in quality of coverage. The American reader will probably find the discussions of the treatment of syphilis quite inadequate, will be confused at the lack of mention of any but British Pharmacopœial preparations, and disappointed at the absence of adequate discussion of the different penicillins and the problem of producing them naturally or synthetically. The literature cited at the end of each chapter is largely British, which is perfectly proper and understandable but not extremely helpful for the American practitioner seeking further information than that given here. It probably is time for an international volume on penicillin.

C. S.

ADVANCING FRONTS IN CHEMISTRY. II. CHEMOTHERAPY. Edited by WENDELL H. POWERS, Assistant Professor of Chemistry, Wayne University, Detroit. Pp. 156; 6 figs. (photographs of contributors). New York: Reinhold Publ. Co., 1946. Price, $3.25.

THIS presents 6 of 7 lectures given at Wayne University in 1945, as a Symposium on Chemotherapy. They are: Chemotherapy in Experimental Tuberculosis, by W. H. Feldman, V.M.D., Sc.D.; Synthetic Antispasmodics, by F. F. Blicke, Ph.D.; Chemistry of the Sulfa Drugs, by E. H. Northey, Ph.D.; The Antimalarial Problem, by H. S. Mosher, Ph.D.; Organometallic Compounds as Chemotherapeutic Agents, by C. K. Banks; Past Developments and Present Needs in the Chemotherapy of Parasitic Diseases, by Col. W. H. Wright, V.M.D., Ph.D. The 7th lecture was on Antibiotics, by Dr. H. E. Carter; actually the first of the series, it could not be prepared in time for publication, which is already more than a year after presentation. Feldman makes a good case for the value of the disulfone derivatives (Promin, Promizole, Diasone) against tuberculosis in guinea pigs but he clearly states that the results of trials in human patients are "not comparable to the striking results obtained in guinea pigs or to the dramatic effects with chemotherapeutic drugs in the treatment of patients who had such an acute disease as pneumococcus pneumonia." The inclusion of Synthetic Antispasmodics here is not covered by the definition of Chemotherapy used by the other contributors, nor is it justified by the brevity of the material presented. Northey's chapter on the sulfonamides is complete, well documented and up to date. Mosher's approach to the antimalarial problem is that

of an organic chemist whose interest lies in methods of synthesis; the recent synthesis of quinine is not covered nor is the now available result of the extensive work done along these lines under the O. S. R. D. during the war. Banks' chapter on the metals is a brief and reasonably adequate summary of the development of organic derivatives of arsenic, bismuth, antimony, mercury and silver. Col. Wright's chapter is long (41 pages), but it is the only part of the book that is likely to be valuable to the practitioner. C. S.

SQUINT AND CONVERGENCE. By M. A. STUTTERHEIM. Pp. 95; 41 ills. London: H. K. Lewis, 1946. Price, $3.00.

FROM start to finish, this book is a compilation of loosely thought-out ideas, badly expressed. The author is correct in his statement that at present we know very little about concomitant squint; but his original thoughts on the subject have meager foundations of fact and he blithely passes by all facts which are not in conformity with his theory. The book is of interest because of its novelty, but it cannot be regarded as a serious exposition of the subject. It is the type of book which usually comes from the pen of non-medical practitioners, and should only be read by someone with sufficient intelligence and background to interpret it critically. F. A.

DISEASES OF THE RETINA. By HERMAN ELWYN, M.B. Pp. 587; 170 ills., 19 in color. Philadelphia: Blakiston, 1946. Price, $10.00.

THIS is a comprehensive text of those diseases of the eye of which the chief manifestations are in the retina, and of the retinal manifestations of general disease. Part I deals with diseases of the retina resulting from disturbances in circulation, and deals extensively with the hypertensive retinopathies. The Author has written extensively on this subject in recent journals; in view of his authoritative position, it is surprising to find no mention made of Wagener's work in this section. His views on the origin of the retinopathy in diabetes are original; and, although they may not be accepted generally, are stimulating.

Part II deals with diseases of the retina resulting from vascular malformations. He includes in this section a description of Coat's disease, which is again based on an original point of view that the fundamental pathologic factor in Coat's disease is a vascular malformation involving the small vessels with the formation of miliary aneurysms. The changes in these small vessels are interpreted by Elwyn to conform to our conception of a telangiectasis. Sturge-Weber disease is also included in this section. Elwyn believes the glaucoma found in this disease, as part of the clinical picture, is due to an angioma of the choroid.

Part III deals with the degenerative diseases of the retina on an hereditary basis. Part IV deals with inflammatory diseases of the retina; Part V with tumors of the retina; Part VI with diseases of the retina leading to retinal detachment; Part VII with developmental anomalies of the retina, and Part VIII describes radiation injuries of the retina.

The book is carefully written and well illustrated and is an outstanding contribution to our literature. It will be useful not only to the ophthalmologist, but also to the neurologist, the internist and the general practitioner, for the ophthalmoscope has now become part of the diagnostic equipment of all well-trained physicians. F. A.

PERIPHERAL VASCULAR DISEASES. By EDGAR V. ALLEN, B.S., M.A., M.D., M.S., F.A.C.P.; NELSON W. BARKER, B.A., M.D., M.S., F.A.C.P.; and EDGAR A. HINES, JR., M.D., B.S., M.A., M.S., F.A.C.P., with Associates in the Mayo Clinic and Mayo Foundation. Pp. 871; 386 ills. Philadelphia: Saunders, 1946. Price, $10.00.

THIS important book will be of value to the physician in general practice, the specialist in peripheral vascular disease, and the research worker. It contains an unusually complete presentation of the basic anatomy and physiology. The clinical material is based upon the wide experience of the authors, working in the Mayo Clinic, and contains an excellent review of the pertinent literature. Care is taken to distinguish between that which can be considered established, that which is opinion, and that which is mere hearsay. The illustrations are excellent and well chosen. While

the text is long for complete reading, an adequate index facilitates reference. It is highly recommended. J. G.

THE NORMAL ENCEPHALOGRAM. By LEO M. DAVIDOFF, M.D., and C. G. DYKE, M.D. Pp. 232; 155 ills. Philadelphia: Lea & Febiger, 1946. Price, $5.50.

THIS is an exceptionally well-handled treatise on the technique of pneumo-encephalography and on the interpretation of the films obtained from the procedure. The most valuable information presented is the clear and direct correlation between the anatomic brain structures and their respective representations to shadows on the Roentgen ray film.

The untimely death of Dr. Dyke is indeed regrettable. Without him we are deprived of the sequel of this work; namely, the abnormal encephalogram. J. C.

LA CULTURA IN VITRO DEL MIDOLLO OSSEO, Problemi di Fisiopatologia Ematologica Studiati con la Tecnica della Cultura dei Tessuti. By AMINTA FIESCHI and GIOVANNI ASTALDI. Preface by CESARE FRUGONI. Biblioteca Hæmatologica, VIII, Directed by ADOLOFO FERRATA. Pp. 309; 123 text figs. and 10 plates in color. Pavia: Tipografia del Libro, 1946. Price not given.

DURING the decade in which the senior author of this book has been a student of the tissue culturing of the hematopoietic organs, she has elaborated a new method which in her hands appears to give special advantages and permits combination with the Warburg technique for the investigation of tissue metabolism. Though she has paid special attention to the megaloblasts, pernicious anemia, and the leukemias, the 10 chapters cover various other phases of the subject, Cooley's anemia, for example. The old question of the genesis and evolution of the megaloblast furnishes an illustration of the capable way in which the subject matter is handled; being pupils of Ferrato, the authors perhaps naturally straddle the dilemma by upholding its evolution into a normoblastic-like cell.

The illustrations, as we have come to expect in Italian works on hematology, are excellent and demonstrate the technical skill shown both in the preparations and the reproductions. These illustrations, together with the fortunate similarity of hematologic terms in Italian and English, make this volume of considerable value even to those who do not read Italian.

The purely morphologic approach to hematologic problems—carried to its extreme by the Germanic school of the past generation led by Naegeli and Pappenheim—has long been recognized as inadequate for further progress. Studies like this one—and we are pleased to see in the Bibliography the number of references to the functional approach written in English—augur well for the further progress in hematology along new dynamic approaches. E. K.

ALLERGY. By ERICH URBACH, M.D., and PHILIP M. GOTTLIEB, M.D. 2nd ed. Pp. 968; 412 ills. New York: Grune & Stratton, 1946. Price, $12.00.

BECAUSE of the great amount of recent work in this field, the new edition represents extensive revision, with many new references and illustrations. Among the additions are sections on psychosomatic allergy, Rh factor, and allergic bronchitis. The important section on drug allergy has been enlarged and brought up to date, and descriptions of test methods have been amplified. The new format is attractive.

This is a valuable book and is strongly recommended. M. McC.

THE HUMAN FRONTIER. By ROGER J. WILLIAMS. Pp. 314; 5 figs. New York: Harcourt, Brace, 1946. Price, $3.00.

THIS book is by the biochemist who discovered and synthesized pantothenic acid of the B vitamin group, and who now wants man studied in his entirety rather than separate parts. Urging the need for many more trained workers, he says: "It will be impossible to make serious advances in psychosomatic medicine as long as man-in-the-abstract remains the consistent theme . . ." The more important chapters are: Fundamental Metabolism as It Is Related to Character Traits. Endocrine Glands and Behavior. Psychological Traits and Capacities. Marriage. Criminology. Heredity and Environment.

If 2 animals who by inheritance should possess like anatomic structures for producing like metabolism the same way, develop

differences in their anatomies, then differences will be shown in their metabolisms. The dozen or more endocrine structures in all probability release some 40 different hormones; the thyroid and pancreas are recognized as producing 1 each, whereas, the pituitary may produce from 6 to 10. The effects of World War II will greatly enhance the future of psychology. The obvious thing about common sense is its wide appeal. In the concrete problem of marriage, the amount of verifiable information is exceedingly scant and fragmentary. Scopolamine, loosely referred to as "truth serum," depresses the higher brain centers, thus rendering the subject unable to "make up a lie or follow through in deception." Hope is expressed for its greater use, together with that of related substances. As to Heredity and Environment, the most promising field for study is identical twins, reared in different environments. Forthrightly, we are told of our shortcomings, which should be stimulating. N. Y.

THE VITAMINS IN MEDICINE. By FRANKLIN BICKNELL, D.M., M.R.C.P., and FREDERICK PRESCOTT, M.Sc., PH.D., A.R.I.C., M.R.C.S., Clinical Research Director, The Wellcome Foundation, London. 2nd ed. Pp. 916; 208 ills. New York: Grune & Stratton, 1946. Price, $12.00.

THIS book is a valuable reference text on the vitamins. It has grown considerably in the 4 years since its first publication in December 1942, having increased from 662 to 916 pages, and from 120 to 208 excellent illustrations. All this despite wartime shortages and restrictions on printing.

The general form is similar to that of the 1st edition. Each vitamin is considered in a separate chapter. The approach is basically clinical but large subdivisions are devoted to such subjects as the history, chemistry, distribution in foods, experimental studies and human requirements, as well as a description of the diseases associated with deficiency, laboratory and therapeutic methods useful in practice. Each part is complete and well written. Documentation is elaborate: there is a large Bibliography at the end of each chapter; the whole totals over 4500 references.

The sections on the vitamin B complex and riboflavin have been rewritten and expanded.

Here has been collected together in an easily readable form a great fund of information otherwise unavailable. As a reference work this book will have important value for both students and practitioners. W. S.

MEDICAL CLINICS OF NORTH AMERICA. Chicago No. Symposium on Advances in Clinical Medicine. January 1947. Pp. 1–258. Phila: Saunders, 1946. Price, $16.00 a year.

THIS volume is prepared especially for the general practitioner. Consequently such common and important conditions as hypertension, coronary disease, nephritis, peptic ulcer, the acute infectious diseases, the dysenteries, pneumonia and rheumatic fever are discussed.

A conservative evaluation of benadryl and pyrabenzamine is made. One clinic is devoted to the action of radioactive phosphorus and the alkylamines in the treatment of neoplastic and allied diseases of the hematopoietic system.

The electrocardiographic studies of Katz and Weinstein are interesting. Chronic hypoparathyroidism; encephalitis disseminated lupus erythematosus, steatorrhea and same phases of psychosomatic medicine are excellently considered. J. W.

UTERINE CONTRACTILITY IN PREGNANCY. By DOUGLAS P. MURPHY, M.D., F.A.C.S., Asst. Prof. of Obstetrics and Gynecology, and Research Associate in the Gynecean Hospital Institute of Gynecologic Research, Univ. of Penna. Pp. 134; 64 ills. Phila.: Lippincott, 1947. Price, $5.00.

THIS monograph presents Dr. Murphy's extended work in the study of uterine activity in pregnancy and labor.

Over 3000 records have been taken with the Lorand tocograph during pregnancy and labor from 1153 individuals. These tocographic records provide a graphic representation of the frequency and character of uterine contraction and the tonus of the uterus at various periods from the time the uterus is first palpable above the pelvic inlet in pregnancy until the placenta and the fetus have been expelled in labor. The results have been carefully sorted, statistical data based thereon, and conclusions reached which are conservative, and in many phases of the subject, conclusive. The monograph

therefore constitutes an authoritative statement on this very important phase of obstetric physiology. It is a book which should be in the hands of all obstetric teachers, and its comment and suggestions should be of practical use to the obstetric clinician. The reader is impressed so much by the potential clinical value of the Lorand tocograph in the observation of abnormal labor that he wishes this instrument were commonly available for practical usage.

Dr. Murphy states that he set out primarily to study the activity of the uterus in pregnancy. His investigations have shown (1) a period of relative quiescence until the 34th week of gestation or until approximately 6 weeks before term, (2) a period of non-rhythmic activity from the 34th to 39th week of pregnancy, and (3) a period of rhythmic activity which includes the 39th and 40th weeks of pregnancy. Regular, rhythmic contraction during this last period has some bearing upon a prompt normal delivery.

Probably the parts of greatest interest to the clinician are those which have to do with the effect of pituitary extract upon uterine activity, and those which concern primary uterine inertia. No response to pituitary extract before the 7th month has been noted. After that time a certain number of uteri respond in more or less characteristic fashion while others continue completely unresponsive. The response appears to vary with the size of the dosage and with the preëxisting tone of the uterus. The responses may be (1) clonic, (2) incomplete tonic and (3) complete tonic. Unfavorable tonic reactions are avoided by administering the drug where there is high tone of the uterus.

Dr. Murphy's findings in primary uterine inertia concur with those of Lorand in demonstrating inefficient, irregular, feeble uterine activity in this syndrome. He is in accord also with the classification which has been presented by Lorand of 3 types of primary uterine inertia: (1) hypotonic, (2) isotonic and (3) hypertonic, depending upon the degree of uterine tone associated with this condition. The treatment of these various types of inertia is discussed.

There are many other observations and conclusions in this monograph which have clinical as well as academic interest to the specialist in obstetrics. T. M.

RADICAL SURGERY IN ADVANCED ABDOMINAL CANCER. By ALEXANDER BRUNSCHWIG, M.D., Prof. of Surgery, Univ. of Chicago. Pp. 324; 116 ills.; 16 tables. Chicago: Univ. of Chicago Press, 1947. Price, $7.50.

IT is fortunate that surgeons, in general, may concentrate their attention on the immediate surgical problems presented by their patients else many surgical advances would be lost in the inactivity resulting from insoluble philosophic and economic considerations. As a rule, both patients and their families are ready and even eager to have any procedure done that may offer a chance, however slight, for survival so that the decision to attempt wide excision of malignant lesions need not rest upon the surgeon alone.

The author discusses the extension of surgery to include operations on "inoperable" malignant abdominal lesions and is able to present results that certainly justify his decision to operate, for of the 100 patients he reports there are 13 living and well, with an average survival time of 40 months. Most of the operations he describes were of such extent that they may be attempted only by experienced surgeons, so that it can be assumed that it is unnecessary to caution against such radical procedures being undertaken without a well-laid plan of action, both as to the operation and to the care of the patient.

The monograph will be of great interest to all surgeons but of usefulness only to the few who have sufficient training and skill, as well as hospital facilities, to carry out such extensive surgical procedures.

I. R.

OFFICE ENDOCRINOLOGY. By ROBERT B. GREENBLATT, B.A., M.D., C.M., Prof. of Endocrinology, Univ. of Georgia School of Medicine; Director, Sex Endocrine Clinic Univ. Hosp., Augusta, Ga. 3rd ed. Pp. 306; 71 figs. Springfield, Ill.: Charles C. Thomas, 1947. Price, $4.75.

THE 1st edition of this small book appeared in 1941 as an outline guide for office practice in endocrinology, having originally been based on a series of postgraduate lectures by the author. Despite the implication of its title, the 46 short chapters deal almost exclusively with gynecologic endo-

crinology. The text is often repetitive and wordy. Emphasis is uneven and the style varies from the excessively lyrical to almost telegraphic English. The occasional specific endorsement of certain commercial products by name seems in questionable taste. Some of the therapeutic recommendations (*e. g.*, that of the efficacy of orally administered pituitary preparations) appear somewhat extravagant. The unfortunate practice of printing category headings and numerical bibliographic references in identical type is often confusing. The book does not seem to be an important contribution to current endocrinologic literature.

E. R.

PENICILLIN IN SYPHILIS. By JOSEPH EARLE MOORE, M.D., Associate Prof. of Medicine and Adjutant Prof. of Public Health Administration, Johns Hopkins Univ.; Physician-in-Charge, Syphilis Division of the Medical Clinic and Visiting Physician, Johns Hopkins Hosp.; Chairman, Syphilis Study Section, National Institute of Health, U. S. P. H. S.; Chairman, Subcommittee on Venereal Disease, N. R. C. Pp. 284; 58 figs; 52 tables. Springfield, Ill.: Charles C Thomas, 1947. Price, $5.00.

IN the battle of "Scientists Against Time," one of the outstanding developments in medicine during the recent war was the discovery in June 1943, by Mahoney, Arnold and Harris, of the United States Public Health Service, that penicillin had definite antisyphilitic powers. This fact, plus the relatively non-toxic character of the preparation, seemed to be just what was needed for the handling of early syphilis in the Armed Forces. A concentrated cooperative group study of penicillin in syphilis was undertaken by the United States Army, Navy, Public Health Service, and the Committee on Medical Research of the Office of Scientific Research and Development, under the general auspices of a Penicillin Panel appointed by the Subcommittee on Venereal Diseases, National Research Council. In addition, some 25 civilian clinics participated in a program of study of the effect of penicillin in early and late syphilis. Lately, the study has been taken over by the Syphilis Study Section of the National Institute of Health. It is particularly fortunate that Dr. Joseph Earle Moore, who coördinated the various aspects of this program, has prepared this *interim* statement of the present knowledge of the value of penicillin in syphilis therapy. As he has access to much as yet not formally published data, this book is unique in the field in not appearing stillborn. Changeable as is the subject of penicillin in syphilis, the material presented will be still fresh for some time to come. Another valuable feature is that while the author has cited most of the contributions of others, some of the sections represent a definitive personal interpretation on the subject by Moore. A notable example of this is the discussion of the treatment of neurosyphilis.

This book tells the physician what to do as well as what not to do with penicillin in syphilis. Unfortunately, the style of presentation is for the most part too statistical for the average reader. It would at least make the subject more appealing if individual case reports were more generally interlarded through the text and its many graphs.

The author (p. 212) reiterates the statement made by him and Goodwin recommending "*that for the purpose of prevention of prenatal syphilis, metal chemotherapy for the syphilitic mother, whether with early or late (including latent) syphilis, be abandoned and that penicillin be adopted universally instead.*" We believe that this conclusion based on a variety of considerations may become one of the most firmly established results of the penicillin study, but, in a field so young, such dogmaticism may force an otherwise conscientious physician without adequate hospitalization facilities required by penicillin therapy, to adopt a compromise system of penicillin prenatal therapy, which may prove inadequate.

H. B.

PSYCHOBIOLOGIC FOUNDATIONS IN DENTISTRY. By EDWARD J. RYAN, B.S., D.D.S., EDITOR, Oral Hygiene and The Dental Digest. Pp. 131. Springfield, Ill.: Charles C Thomas, 1946. Price, $3.00.

THE healing professions have been dominated to such an extent by the scientific method that common sense observation and understanding of man as an entity rather than a complex of signs and symptoms has tended to be forgotten. Dentistry, with its emphasis on technical excellence and its mechanical appliances, has not infrequently lost sight of the patient toward whose wel-

fare the dentist's knowledge and skill were directed.

Dr. Ryan has had much experience as an editor in writing for large groups of practicing dentists. He writes clearly and presents his subject in an interesting and thought-provoking manner. He has selected wisely from the literature on psychosomatic medicine and has adapted principles for application to dental practice. He is concerned particularly with the reaction of the dental patient to pain and makes suggestions which should be of value to practitioners in meeting this problem. A chapter is devoted to the interpretation of constitutional patterns of disease with particular reference to the influence of emotions upon the tissues of the mouth. Dental disease in the 7 ages of man is discussed and modifications of treatment indicated in every age group are suggested.

This book should be widely read and should stimulate dentists to further study of the principles of psychobiology and their applications to dentistry. P. B.

CONDUCTION ANESTHESIA: CLINICAL STUDIES OF GEORGE P. PITKIN, M.D., edited by JAMES L. SOUTHWORTH, M.D., and ROBERT A. HINGSON, M.D. Pp. 981; 606 ills. Philadelphia: J. B. Lippincott, 1946. Price, $18.00.

FOR years Dr. George Pitkin collected artists' drawings illustrating techniques of regional anesthesia. Thousands of dollars were expended during his lifetime. These plates, skillfully executed and superbly reproduced, form the basis of this volume.

Anatomy is carefully presented in an introductory 212 page section. The pharmacology of local anesthetic agents is discussed, after which detailed considerations of all types of conduction anesthesia are given in the central section of the book. Concluding chapters are devoted to caudal, spinal and refrigeration anesthesia, and there is a final section on the therapeutic applications of nerve block. The format is pleasing, the paper excellent and the only suggestion the Reviewer has as far as the book itself is concerned is that a 2 volume edition would be easier to handle than the rather bulky single volume.

The work should be of real interest to anesthesiologists and to surgeons engaged both in the practice of general surgery or in the surgical specialties such as neurosurgery, otolaryngology, orthopedics and ophthalmology. It certainly is detailed, perhaps too detailed. For example, the discussion of block of the brachial plexus includes a posterior, infraclavicular, axillary, lateral and supraclavicular approach.

The section on spinal anesthesia covers 100 pages. Some statements are made which might be challenged. Thus, the Sylvester method is recommended for production of artificial respiration in instances of respiratory distress and oxygen administration *via* an anesthesia machine is not mentioned. The dosage of procaine for use in obstetrics is given as 100 to 200 mg. which seems excessive.

In the Reviewer's opinion, it constitutes a comprehensive coverage of all forms of regional anesthesia, but its very comprehensiveness may limit its value to all but the specialist. R. D.

NEW BOOKS

Diseases of the Chest, Emphasizing X-ray Diagnosis. By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., and MORRIS RUBIN, B.A., M.D. Pp. 685; 355 ills., 24 in color. Phila. and London: Saunders, 1947. Price, $12.00.

Medical Aspects of Growing Old. By A. T. TODD, M.B. (EDIN.), M.R.C.P. (LOND.). Pp. 164. Balt.: Williams & Wilkins, 1946. Price not given.

Handbook of Medical Emergencies. Contributors: THOMAS B. FITZPATRICK, M.D., JOHN L. BAKKE, M.D., H. STANLEY BENNETT, M.D., EVAN CALKINS, M.D., EDWARD A. CARR, JR., M.D., DEAN P. APPERSON, M.D., WALTER W. POINT, M.D., and JAMES M. STEWART, M.D. Pp. 106. Cambridge: Harvard Univ. Press, 1947. Price, $2.50.

Milk and Food Sanitation Practice. By H. S. ADAMS, D.Sc., Division of Public Health, Minneapolis. Pp. 311; 65 ills. New York: Commonwealth Fund, 1947. Price, $3.25.

Recent Progress in Hormone Research. Proceedings of the Laurentian Hormone Conference. Edited by GREGORY PINCUS. Pp. 399; 29 ills. New York: Academic Press, 1947. Price, $7.50.

Thirteen articles, mostly by well-known investigators, including considerable unpublished material.

Health and Rehabilitation Through Chest Training. By SAMUEL DELANO, A.B., M.D. Pp. 142. New York: William-Frederick Press, 1947. Price, $2.50.

Office Immunology, Including Allergy. Edited by MARION B. SULZBERGER, M.D., and RUDOLF L. BAER, M.D. Pp. 420; 6 ills. Chicago: Year Book Publishers, 1947. Price, $6.50.

THE 17th of the General Practice Manuals.

Psychiatric Research. Papers read at the Dedication of the Laboratory for Biochemical Research, McLean Hosp., Waverly, Mass. By CECIL K. DRINKER, JORDI FOLCH, STANLEY COBB, HERBERT S. GASSER, WILDER PENFIELD and EDWARD A. STRECKER. Pp. 113. Cambridge: Harvard Univ. Press, 1947. Price, $2.00.

Biological Symposia. Estimation of the Vitamins. Vol. XII. Edited by JACQUES CATTELL. Pp. 531. New York: Ronald Press, 1947. Price, $6.50.

THIS volume is a collection of papers by well-qualified investigators dealing with the best recognized vitamin assay methods. The types of biologic assay that use animals, microbiologic methods that use microörganisms, and the physiochemical methods are treated by different authors. The collection fills a gap in the vitamin literature and will be extremely useful for reference in this field. (W. S.)

Hypnotism Today. By LESLIE M. LECRON, B.A., and JEAN BORDEAUZ, B.A., M.A., PH.D., Consulting Psychologists and Psychotherapists. Foreword by MILTON H. ERICKSON, M.D., Director of Psychiatric Research, Wayne County Hosp., Eloise, Mich. Pp. 278. New York: Grune & Stratton, 1947. Price, $4.00.

WRITTEN by 2 psychologists, "Hypnotism Today" is an enthusiastic presentation of the history, theory, technique and practical therapeutic uses of hypnosis. As Dr. Erickson states in the Foreword, the authors "have selected their material well, . . . and their presentation of their own studies is unassuming and straightforward." (W. P.)

NEW EDITIONS

Standard Methods of the Division of Laboratories and Research of the New York State Department of Health. By AUGUSTUS B. WADSWORTH, M.D. With a Foreword by GILBERT DALLDORF, M.D. 3rd ed. Pp. 990; 105 ills. Balt.: Williams & Wilkins, 1947. Price, $10.00.

A Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., with the assistance of WALSH MCDERMOTT, M.D., HAROLD G. WOLFF, M.D. 7th ed. Pp. 1730; 244 ills. Phila., and London: Saunders, 1947. Price, $10.00.

THIS hardy perennial exhibits its customary excellence in spite of the difficulties of wartime. Articles have been inserted on 16 new subjects, and there are some 50 or 60 new write-ups, occasioned by death or retirement of former contributors.

Theory of Occupational Therapy. By NORAH A. HAWORTH, M.A., and E. MARY MACDONALD. Foreword by SIR ROBERT STANTON WOODS, M.D., Physician-in-Charge of Dept. of Physical Medicine, London Hospital. 3rd ed. Pp. 159; 6 ills. Balt.: Williams & Wilkins, 1947. Price, $2.50.

Vascular Disorders of the Limbs. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., etc., Physician-in-Charge of Dept. of Clinical Research, Univ. College Hosp., London. 2nd ed. Pp. 118. New York and London: Macmillan, 1946. Price, $2.25.

Diseases of Metabolism. Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner. Edited by GARFIELD G. DUNCAN, M.D., Director of Med. Div., Penna. Hosp.; Clinical Prof. of Medicine, Jefferson Medical College. 2nd ed. Pp. 1045; 167 figs. Phila. and London: Saunders, 1947. Price, $12.00.

MUCH has transpired in the field of metabolism in the 5 years since the 1st ed. appeared. The most extensive changes are the sections on the Thyroid Gland, the Kidneys, the Blood, the Endocrines, Alloxan Diabetes.

The Principles and Practice of Medicine. (Originally written by WILLIAM OSLER.) By HENRY A. CHRISTIAN, A.M., M.D., LL.D., etc. Hersey Prof. of the Theory and Practice of Physic, etc. 16th ed. Pp. 1539. New York and London: D. Appleton-Century, 1947. Price, $10.00.

VIGOROUSLY proceeding into its second semicentennial, this classic among medical textbooks remains the leading exponent in its field of single authorship. It has kept well abreast of the considerable additions to medical knowledge since the last edition (1944), with preservation of a "continuity of thought and a balance in description" difficult to obtain in books written by a large body of authors.

Clinical Practice in Infectious Diseases. By E. H. R. HARRIES, M.D. (LOND.), F.R.C.P., and M. MITMAN, M.D. (LOND.) F.R.C.P. 3rd ed. Pp. 679. Balt.: Williams & Wilkins, 1947. No price given.

Pye's Surgical Handicraft. Edited by HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hosp., London, etc. 15th ed. Pp. 668; 789 ills. Balt.: Williams & Wilkins, 1947. Price, $6.00.

THIS manual, first published in 1884, is a practical, well-illustrated handbook that contains in brief form a vast quantity of information. The surgical resident in America will find it somewhat lacking in its neglect of physiologic principles, as for example the nutrition of a patient with decubitus ulcers; but any resident can profit from studying the technical aids described for the care and comfort of patients.

Diseases Transmitted from Animals to Man. By THOMAS G. HULL, Ph.D., Director, The Scientific Exhibit American Medical Association. 3rd ed. Pp. 571; 75 ills. Springfield, Ill.: Charles C Thomas, 1947. Price, $10.50.

Pulmonary Tuberculosis. By R. Y. KEERS and B. G. RIGDEN, of the Red Cross Sanatoria of Scotland. 2nd ed. Pp. 277; 124 ills. Balt.: Williams & Wilkins, 1946. Price, $5.00.

THIS small volume, intended by the authors as a handbook for the student and general practitioner, admirably serves its purpose. In 15 brief and concise chapters a summary of the essential knowledge on diagnosis and management of pulmonary tuberculosis is presented. It contains 114 excellent reproductions of chest roentgenograms illustrating the use of Roentgen ray in the differential diagnosis, assessment of progress, and therapy of tuberculosis.

Psychopathology. A Survey of Modern Approaches. By J. ERNEST NICOLE, O.B.E., L.M.S.S.A., D.P.M.R.C.P.C.S., Medical Supt., Winwick Mental Hospital. 4th ed. Pp. 268. Balt.: Williams & Wilkins, 1946. Price, $4.75.

THIS handbook reviews briefly the different approaches to psychopathology. Freud and McDougall are given about the same space and physiologic and ethnologic findings are considered along with the theories of Kempf, Rivers, Watson, Kretschner. The outlines are clear and brief and there are useful cross-references. The Bibliography is extensive.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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